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Emerging Therapeutic Options for Platinum-Sensitive Ovarian Cancer Patients

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Abstract: Ovarian cancer is a relatively infrequent malignancy, but it is the fifth leading cause of cancer-related mortality in American women. The initial diagnosis of ovarian cancer is usually made when the disease is at an advanced stage. Although advanced ovarian cancer is characteristically sensitive to initial surgical debulking followed by platinum-based combination chemotherapy, it is rarely cured, and even patients who achieve a complete remission ultimately go on to experience relapsed disease. When tumor relapse occurs more than 6 months following completion of the platinum-based treatment, patients are defined as having platinum-sensitive disease. This roundtable includes an expert discussion of the options for treatment of patients with platinum-sensitive ovarian cancer. After distinguishing this form of recurrent ovarian cancer from platinum-resistant and platinum-refractory disease, the therapeutic options are reviewed. Much evidence supports the benefit of secondary cytoreductive surgery in platinum-sensitive patients, although this strategy has not yet been established by a prospective randomized clinical trial. Further, the standard chemotherapy regimens recommended in this setting are reviewed in the context of the clinical trials that established their efficacy. Finally, a description of emerging and investigational treatments, including both biologic agents and novel cytotoxic drugs, is included. Several recent and ongoing clinical trials involving these investigational agents are described. Throughout, the experts discuss the implication of these findings in the clinical setting.

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Target Audience

This activity has been designed to meet the educational needs of oncologists and other health care professionals who treat patients with ovarian cancer.

Statement of Need/Program Overview

Ovarian cancer is a considerable therapeutic challenge for clinicians, and outcomes for the disease have not changed dramatically for several decades. This year, more than 20,000 women in the United States will be diagnosed with ovarian cancer, and nearly 14,000 will succumb to the disease. When tumor relapse occurs more than 6 months following completion of platinum-based treatment, patients are defined as having platinum-sensitive disease. New therapies, new combinations of existing chemotherapies, and new methods of delivery of local and systemic therapies have been shown to improve survival for patients with ovarian cancer. Many issues surround the management of ovarian cancer, such as the utility of CA-125 testing, choice of agent(s), use of monotherapy versus combination regimens, and the timing of salvage therapy.

Educational Objectives

After completing this activity, the participant should be better able to:

- Recognize biologic pathways of significance in ovarian cancer pathogenesis and resistance
- Evaluate current and emerging treatment options in the management of ovarian cancer patients who have relapsed
- Develop an appropriate regimen for patients with either newly diagnosed or recurrent ovarian cancer
- Discuss toxicity prevention, identification, and management strategies for patients receiving therapy for ovarian cancer

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Overview of Ovarian Cancer

Deborah K. Armstrong, MD

Introduction

In the United States, approximately 21,880 cases of ovarian cancer were diagnosed in 2010, and 13,850 women died from the disease.[1] Ovarian cancer is the ninth most common cause of new female malignancies but the fifth leading cause of cancer-related deaths.[1] Additionally, ovarian cancer is the leading cause of death from gynecologic cancers.[2] Based on data from the Surveillance Epidemiology and End Results (SEER) program from 2003 to 2007, the age-adjusted incidence rate for ovarian cancer is 12.9 per 100,000 women per year.[3] Women have a 1 in 72 chance of being diagnosed with ovarian cancer during their lifetime; 1.39% of women who are born today will be diagnosed with ovarian cancer. The incidence of ovarian cancer increases with age. The median age at diagnosis is 63 years, and the median age at ovarian cancer death is 71 years. The age-adjusted death rate is 8.6 per 100,000 women per year.

Several risk factors for ovarian cancer have been identified in the published literature. Interestingly, women who were younger (≤25 years of age) at the time of their first pregnancy and birth have a decreased risk of developing ovarian cancer.[4] In contrast, women who either do not have children or were older (>35 years of age) at the time of their first pregnancy and birth have a higher risk of developing the malignancy. Other factors that may decrease a woman's chance of developing ovarian cancer include the use of oral contraceptives and breastfeeding. Hormone therapy has recently been proposed as being associated with an increased risk of ovarian cancer. In a study of nearly 1 million women with an average follow-up of 8.0 years, current use of hormone therapy was associated with an incidence rate ratio of 1.44 (95% confidence interval [CI], 1.30–1.58) for epithelial ovarian cancer.[5] This incidence rate decreases with years since last use of hormone therapy, from 1.22 (95% CI, 1.02–1.46) for women who are 2 years or less from their last use to 0.63 (95% CI, 0.41–0.96) for women who are more than 6 years beyond their last use. Although mutations in *BRCA1* and *BRCA2* are associated with early-onset disease, only a minority of patients have these mutations.[6]

The overall 5-year relative survival for patients with ovarian cancer is 45.6%, but most of these deaths occur as a result of metastatic disease.[3] In fact, patients with only localized or regional disease at diagnosis have a 5-year relative survival of 93.5% or 73.4%, respectively, reflecting the ability to treat and even cure early-stage disease. Comparatively, patients diagnosed with metastatic ovarian cancer have a 5-year relative survival of 27.6%, often suffering disease relapse and, ultimately, death. Unfortunately, patients diagnosed with metastatic disease comprise the majority (62%) of ovarian cancer patients at diagnosis, and only 15% and 17% of patients have localized or regional disease at diagnosis, respectively.

The high incidence of patients diagnosed with advanced-stage disease is largely explained by the lack of a screening test for ovarian cancer that is equivalent in ability to a mammogram for breast cancer or a Pap smear for cervical cancer. Currently, no screening methods for the population are either recommended in professional guidelines or approved by the US Food and Drug Administration (FDA). A symptom index has been proposed to identify patients with ovarian cancer; this symptom index includes bloating or increased abdominal size ($P<.001$), pelvic or abdominal pain ($P<.001$), difficulty eating or quickly feeling full ($P=.010$), and urinary urgency or frequency.[7] These symptoms were especially associated with ovarian cancer when they were new (present <1 year) and frequent (>12 days/month). The sensitivity of this symptom index was 56.7% for early-stage disease and 79.5% for advanced-stage disease, and the specificity was 90% for women older than 50 years and 86.7% for women younger than 50 years. However, separate studies have suggested lower rates of sensitivity and specificity.[8,9] A randomized trial in the United States failed to show a benefit associated with using ultrasound to detect early-stage ovarian cancer,[10] although initial data from a United Kingdom study suggests ultrasound may be beneficial in this setting.[11] Similarly, assessment of cancer antigen 125 (CA-125) levels have not yet proved to be significant for ovarian cancer screening.[11,12] However, data from a prospective single-arm screening trial were presented at the 2010 American Society of Clinical Oncology (ASCO) Annual Meeting, suggesting that use of a Risk of Ovarian Cancer Algorithm (ROCA) that incorporates change in CA-125 levels over time as well as patient age, followed by referral to transvaginal sonography, was a feasible screening strategy for women older than 50 years (99.7% specificity; 95% CI, 99.5–99.9).[13] The use of other biomarker-based algorithms remains controversial and is not recommended as a routine screening practice.

Ovarian cancer is one of the few solid tumors that responds well to surgery even in the setting of advanced disease. Although ovarian cancer may spread to distant sites via the bloodstream and/or nodal system, most of the

disease is restricted to the peritoneal cavity. This allows relatively easy surgical access to much of the disease, and significant surgical debulking can be achieved. Interestingly, endocrine responsive pathways that are typically active in ovarian cancer may allow debulking in one region to affect the disease in another area.[14] For these reasons, cytoreductive surgery with maximal removal of all gross disease is recommended as initial treatment for patients with clinical stage II–IV.[2] Additionally, patients with advanced disease may have an increased overall survival (OS) if they also undergo a systematic lymphadenectomy.[15]

Standard chemotherapy following surgery for patients with newly diagnosed ovarian cancer remains a combination of a platinum agent with a taxane.[2] Fortunately, most patients respond to this initial treatment and in fact often achieve clinical complete remission (CR). Several prognostic factors can be used to determine if a patient is likely to achieve CR, including extent of surgery, disease stage, histologic cell type and degree of differentiation, patient age, and presence of high-volume ascites.[16-19] Of these, the extent and success of surgical debulking are potentially among the most important factors.

It should be noted that, in general, the discussion here that revolves around epithelial ovarian cancer is also applicable to fallopian tube cancers and primary peritoneal cancers. Additionally, many of the studies in the ovarian cancer field include patients with each of these diseases.

Recurrent Disease

After completing surgery and initial chemotherapy treatment, patients achieving a CR undergo observation with routine follow-up. For patients with ovarian cancer, clinical CR is defined as having no objective evidence of disease, including no obvious signs on physical examination, negative CA-125 levels, and a negative CT with lymph nodes of less than 1 cm.[2] Follow-up generally consists of imaging studies, including chest/abdominal/pelvic computed tomography (CT), magnetic resonance imaging, positron emission tomography (PET), PET-CT, and/or chest imaging. Further, assessment of CA-125 at each follow-up evaluation is indicated if the baseline CA-125 level was elevated.[2] The median time of disease relapse following an increase in CA-125 levels ranges from 2 to 6 months. Initiating therapy on the basis of a rise in CA-125 levels alone is controversial. Results of a recently published randomized trial suggest no OS benefit associated with treatment of relapse on the basis of a rise in CA-125 levels alone.[20] In this study, ovarian cancer patients (N=1,442) who achieved a CR following first-line platinum-based chemotherapy underwent clinical evaluation and CA-125 measurement every 3 months. Patients identified as having a rise in CA-125 levels (defined as >2 times the upper limit of normal) were randomized to either early chemotherapy administered within 28 days of CA-125 detection or delayed chemotherapy administered at clinical or symptomatic relapse. After a median follow-up of 56.9 months, no significant change in OS was evident between the early and delayed treatment groups (hazard ratio [HR] 0.98, 95% CI, 0.80–1.20; *P*=.85). Median OS from the time of randomization was 25.7 months and 27.1 months for patients in the early and delayed treatment groups, respectively. It should be noted that the patients in this trial experienced relapse earlier than typically observed in the clinical setting; additionally, these results may not be directly applicable to patients with platinum-sensitive recurrent ovarian cancer.

Definition and Frequency of Platinum-Sensitive Disease

Patients who progress on initial platinum-based chemotherapy are considered platinum-refractory. Ovarian cancer that has relapsed after initial treatment with a platinum-based chemotherapy regimen is defined by its platinum sensitivity.[21] The distinction between platinum-sensitive and platinum-resistant recurrent ovarian cancer is made on the basis of time from completion of initial chemotherapy.[22,23] Those patients who initially respond to platinum-based chemotherapy but who experience disease recurrence within 6 months of completing treatment are considered platinum-resistant. In contrast, patients with disease recurrence that manifests 6 months or more after completing therapy are considered platinum-sensitive. The 6-month window is not clinically significant, it is merely a time marker that has become typically used in the clinical trial setting. However, it is based on the observation that while re-treatment with a platinum agent is fairly effective in patients relapsing after 6 months, re-treatment in patients relapsing within 6 months generally produces a response rate of less than 10%, and other chemotherapeutic agents are more effective.

Compared with platinum-sensitive patients, the prognosis for platinum-refractory and platinum-resistant patients is poor. Thus, clinical trials are an important strategy for the management of these patients. Interestingly, patients with *BRCA1* or *BRCA2* mutations are more likely to have platinum-sensitive disease. Mounting evidence suggests that while these mutations may predispose the individual to developing ovarian cancer, they are also responsible for making the malignancy more responsive to treatment with a platinum-based chemotherapy.[24,25] However, although these patients typically have superior progression-free survival (PFS) and OS, generally manifested as maintaining the platinum-sensitivity for a longer period of time, they do eventually go on to develop platinum-resistant or platinum-refractory ovarian cancer.

If disease recurs after a patient undergoes optimal debulking surgery, it is likely that she is platinum-sensitive. However, if a patient was not completely debulked,

it is likely that she will experience disease recurrence within 6 months after completion of chemotherapy, especially if she had advanced disease at diagnosis. For example, a combined exploratory analysis of 3 prospective randomized clinical trials (N=3,126) showed that patients with complete surgical resection had significant improvements in both OS and PFS compared with patients who had any macroscopic residual tumor.[17] Complete resection was associated with a 66% decreased risk of progression and a 68% decreased risk of mortality. The impact of surgery on OS and PFS remained significant regardless of patient age, disease stage, tumor grade, and the presence of ascites.

Concerns for Platinum-Sensitive Patients

A number of issues should be considered in the management of patients with platinum-sensitive ovarian cancer. One of these is that because these patients often undergo multiple cycles of platinum-based combination chemotherapy, they are at increased risk for developing treatment-related toxicities. Some patients do develop allergies to platinum agents; in one study, this was demonstrated to occur in approximately 16% of recurrent ovarian cancer patients treated with carboplatin.[26] These allergic reactions typically occur during the first or second cycle of platinum-based chemotherapy for recurrent disease, or around the eighth cycle the patient has received in total (including initial treatment).[27] Allergic reactions, especially serious reactions such as life-threatening anaphylaxis, can be quite frightening for the patient. Symptoms of an allergic reaction to a platinum agent include rash, edema, shortness of breath, chest pain, tachycardia, hives and itching, blood pressure changes, nausea, vomiting, chills, and bowel function changes.[26] Although the offending platinum agent should never be used again in patients with serious allergic reactions, desensitization protocols have been established for patients with less serious allergies.[28] The vast majority (90%) of patients who exhibit a platinum allergy can successfully be desensitized and undergo re-treatment with the platinum agent. These patients often receive a slower infusion rate for future doses of carboplatin, sometimes requiring hospitalization for administration.

Another issue to consider in the treatment of relapsed platinum-sensitive ovarian cancer is the aggressiveness of subsequent rounds of combination chemotherapy. Although most of these patients will respond to treatment and achieve a second CR, the majority of these remissions are even shorter than the first remission. Thus, the treatment-free intervals these patients experience become progressively shorter. Eventually, these patients go on to become classified as having platinum-resistant or platinum-refractory disease.

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Current Treatment Approaches for Platinum-Sensitive Ovarian Cancer Patients

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Surgical Options

Secondary cytoreductive surgery may be performed when a diagnosis of recurrence has been made after an extended (≥6 months) disease-free interval.[1] For clarity, secondary cytoreduction in the context of this discussion refers to those procedures performed with the intent of removing recurrent disease made apparent after a disease-free interval. This is in distinction to those surgeries performed at the conclusion of first-line chemotherapy to determine the extent of disease and surgeries performed to treat a complication from recurrent disease, such as a bowel obstruction.

Several lines of evidence suggest that the benefit of surgery in ovarian cancer remains closely associated with chemosensitivity, even in patients with recurrent disease. This observation is based on the hypothesis that cytoreductive surgery improves patient outcomes by reducing the tumor bulk and with it the population of chemotherapy-resistant cells. However, the efficacy of this strategy in the recurrent setting remains to be conclusively demonstrated in prospective, randomized trials. Instead, data from retrospective and single-arm studies exist. For example, in a study of ovarian cancer patients (N=106) who underwent secondary cytoreductive surgery following a disease-free interval of more than 6 months, complete cytoreduction was found to maximize survival compared with surgeries leaving residual disease (median OS, 44.4 vs 19.3 months; P=.007).[2] In another similarly designed study (N=60), complete cytoreduction was again associated with a significant improvement in median OS compared with suboptimal resection.[3] In a more recent meta-analysis (N=2,019), only complete secondary cytoreductive surgery was significantly independently associated with improved overall postoccurrence survival time (P=.019).[4] Prognostic factors have been examined to identify those patients most likely to benefit from secondary cytoreductive surgery; such factors include a disease-free interval of more than 12 months (P<.01) and minimal residual disease (<2 cm) after a prior cytoreductive surgery (P<.02).[5] In this study, optimal secondary cytoreduction was again associated with a significantly prolonged median OS compared with suboptimal secondary cytoreduction (30 vs 17 months; P<.05).

An area of significant controversy remains regarding patients with so-called intermediate sensitive disease (ie, those patients who recur within 6–12 months after completion of first-line chemotherapy). In one study, it was shown that patients who underwent secondary cytoreductive surgery prior to second-line chemotherapy had significantly prolonged survival times compared with patients who were given preoperative second-line chemotherapy (median OS, 48.4 vs 24.9 months; P=.005).[2] The OS disadvantage associated with second-line treatment prior to second cytoreductive surgery may be due to the selection for surgery of those patients with disease exhibiting acquired resistance to cytotoxic chemotherapeutic agents.

The role of secondary cytoreductive surgery for the treatment of recurrent ovarian cancer is currently under investigation in 3 ongoing prospective randomized clinical trials. The European Organization for Research and Treatment of Cancer (EORTC) study 55963 is a randomized, phase III trial (expected, N=700) comparing platinum-based chemotherapy alone versus chemotherapy followed by secondary cytoreductive surgery.[6] The Gynecologic Oncology Group (GOG) 213 study is a randomized, phase III trial (N=660) comparing carboplatin/paclitaxel treatment alone or in combination with bevacizumab fol-

lowed by bevacizumab and secondary cytoreductive surgery.[7] DESKTOP III (A Randomized Multicenter Study to Compare the Efficacy of Additional Tumor Debulking Surgery vs Chemotherapy Alone in Recurrent Platinum-Sensitive Ovarian Cancer) is a randomized, multicenter, phase III trial (expected, N=408) comparing maximal secondary cytoreductive surgery followed by platinum-based combination chemotherapy versus chemotherapy alone in platinum-sensitive ovarian cancer patients.[8]

Platinum-Based Chemotherapeutic Options

Overall, the chemotherapy options for platinum-sensitive patients can be described as either single agent versus combination regimens, and inclusion versus exclusion of a platinum agent.

For patients with platinum-sensitive ovarian cancer, re-treatment with a platinum agent is a common therapeutic strategy. This approach is recommended by the National Comprehensive Cancer Network (NCCN).[1] A number of platinum-based combination chemotherapy regimens are recommended in this setting, including carboplatin/paclitaxel, carboplatin/weekly paclitaxel, carboplatin/docetaxel, carboplatin/gemcitabine, carboplatin/liposomal doxorubicin, and cisplatin/gemcitabine. The use of these regimens in the setting of platinum-sensitive ovarian cancer is supported by a number of large, randomized clinical trials. In a large meta-analysis, platinum-based combination chemotherapy was associated with varying significant improvements in response rates, PFS, and OS when compared with single-agent chemotherapy (either carboplatin or paclitaxel).[9]

The ICON4/AGO-OVAR-2.2 trial was an international, multicenter, randomized clinical study that enrolled patients (N=802) between 1996 and 2002.[10] Patients were randomized to receive either paclitaxel plus platinum chemotherapy or conventional (largely single-agent) platinum-based chemotherapy. After a median follow-up of 42 months, a significant benefit in OS was apparent in patients treated with paclitaxel plus platinum chemotherapy (HR 0.82, 95% CI, 0.69–0.97; *P*=.02). This corresponded to a 7% improvement in the absolute difference in 2-year OS (57% vs 50%), and a 5-month improvement in the median OS (29 vs 24 months). PFS was also similarly improved in patients receiving paclitaxel plus platinum chemotherapy compared with patients receiving conventional chemotherapy (HR 0.76, 95% CI, 0.66–0.89; *P*=.0004).

The combination of carboplatin/gemcitabine is currently the only FDA-approved regimen for platinum-sensitive recurrent ovarian cancer and was established in an intergroup trial of the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR), the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG), and the EORTC Gynecological Cancer Group (GCG).[11] In this study, patients (N=356) were randomized to receive either carboplatin/gemcitabine or single-agent carboplatin, both administered every 21 days. After a median follow-up of 17 months, the median PFS (primary endpoint) was significantly prolonged in patients receiving carboplatin/gemcitabine compared with carboplatin alone (8.6 vs 5.8 months; HR 0.72, 95% CI, 0.58–0.90; *P*=.0031). Similarly, the response rate was also significantly improved for patients who received gemcitabine (47.2% vs 30.9%; *P*=.0016). However, this study failed to show an OS benefit for patients receiving the combination chemotherapy versus the single-agent regimen (HR 0.96, 95% CI, 0.75–1.23; *P*=.7349).

The efficacy of the combination of carboplatin/liposomal doxorubicin was demonstrated in a phase III, randomized, multicenter noninferiority trial in which it was compared with carboplatin/paclitaxel in patients (N=976) with platinum-sensitive recurrent ovarian cancer.[12] Because of the large study population, both noninferiority and superiority analyses were able to be assessed in this trial. After a median follow-up of 22 months, PFS was found to be not only noninferior to paclitaxel/carboplatin, but also significantly superior (11.3 vs 9.4 months: HR 0.821, 95% CI, 0.72–0.94; *P*=.005). One especially interesting result in this study was the ability to establish a PFS risk stratification based on the number of baseline predictive factors. Factors found in multivariate analysis to be significant for a longer PFS included a therapy-free interval of longer than 12 months (*P*<.001), lack of measurable disease (*P*<.001), a CA-125 level below 100 U/mL (*P*<.001), and treatment with carboplatin/liposomal doxorubicin (*P*=.003). Importantly, patients with the highest risk for progression essentially had a very similar outcome regardless of the treatment arm to which they were assigned. In contrast, patients with a more favorable prognosis (low risk for progression) had a significantly higher rate of difference between the 2 treatments. This outcome suggests that platinum-sensitive patients may be risk-stratified to determine those individuals most likely to benefit from the carboplatin/liposomal doxorubicin combination. Despite the fact that all patients enrolled in this study had previously received first-line treatment with a platinum plus taxane combination, toxicities were found to be manageable. Hematologic toxicities occurred at a similar frequency between the 2 treatment groups; more patients in the carboplatin/liposomal doxorubicin arm experienced grade 3/4 neutropenia (45.7% vs 35.2%), whereas more patients in the carboplatin/paclitaxel arm experienced grade 3/4 thrombocytopenia (15.9% vs 6.2%). More patients in the carboplatin/liposomal doxorubicin arm experienced a grade 3/4 nonhematologic adverse event compared with patients in the carboplatin/paclitaxel arm (36.8% vs 28.4%; *P*=.001),

with the exception of carboplatin hypersensitivity reactions, which were significantly reduced (Grade 2–4, 5.6% vs 18.8%; *P*<.001).

Non–Platinum-Based Chemotherapeutic Options

In addition to platinum-based chemotherapy regimens, other agents have been investigated in the context of platinum-sensitive disease. Most randomized studies evaluating therapeutic agents for second-line or subsequent therapy include both platinum-sensitive and platinum-resistant cohorts; however, the cohorts of platinum-sensitive patients are sufficiently large to allow inferences.

Single-agent pegylated liposomal doxorubicin was evaluated in a randomized multicenter phase III trial of patients (N=474) with either platinum-sensitive or platinum-resistant recurrent ovarian cancer.[13,14] In this study, patients were randomized to receive either pegylated liposomal doxorubicin or topotecan. Significantly for platinum-sensitive patients (N=220), the pegylated liposomal doxorubicin group experienced a 30% reduction in the risk of death compared with patients in the topotecan group (median OS: 107.9 vs 70.1 weeks; HR 1.432, 95% CI, 1.066–1.923; *P*=.017). Interestingly, this survival benefit was observed despite relatively similar response rates between the 2 treatment groups (19.7% vs 17.0%; *P*=.390).

Pegylated liposomal doxorubicin has also been evaluated in combination with the investigational cytotoxic agent trabectedin. In a phase III, randomized trial that included 214 patients with "partially platinum-sensitive" ovarian cancer (defined as recurring after a platinum-free interval of 6–12 months), the pegylated liposomal doxorubicin/trabectedin combination was compared with pegylated liposomal doxorubicin alone.[15] Patients treated with the combination achieved a 35% reduction in the risk of disease progression or death (HR 0.65, 95% CI, 0.45–0.92; *P*=.0152), as well as a 41% reduction in the risk of death alone (HR 0.59, 95% CI, 0.43–0.82; *P*=.0015). Interestingly, patients who received pegylated liposomal doxorubicin/trabectedin had a significantly prolonged median OS following subsequent re-treatment with a platinum agent (13.3 vs 9.8 months; HR 0.63; *P*=.0357). This result was analyzed in further detail, and it was found that patients treated with the pegylated liposomal doxorubicin/trabectedin combination had a median delay of 2.5 months before receiving subsequent chemotherapy as compared with patients receiving single-agent pegylated liposomal doxorubicin.[16] A phase III clinical trial compared single-agent topotecan with either topotecan/etoposide or topotecan/gemcitabine in patients (N=502) with either platinum-resistant or platinum-sensitive disease (N=294).[17] The addition of a second agent to topotecan had no significant effect on survival, with similar median OS in each of the 3 arms (17.2, 17.8, and 15.2 months, respectively; *P*=.7647 for topotecan versus topotecan/etoposide and *P*=.2344 for topotecan versus topotecan/gemcitabine). Similarly, there were no differences among the 3 treatment groups in either median PFS (7.0, 7.8, and 6.3 months, respectively) or the rate of objective response (27.8%, 36.1%, and 31.6%, respectively). However, those patients who received either of the combination regimens were more likely to experience severe thrombocytopenia.

Other Treatment Options

Several agents are emerging for the treatment of platinum-sensitive ovarian cancer. One agent that has been especially investigated in the context of platinum-sensitive versus platinum-resistant disease is the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab.

The GOG 170D study was a phase II trial that recruited both platinum-sensitive and platinum-resistant patients (N=62).[18] Patients received single-agent bevacizumab until disease progression or unacceptable toxicity. A 21.0% clinical response rate was reported, with 40.3% of patients remaining progression-free for at least 6 months. The median PFS was 4.7 months, and the median OS was 17 months. In an exploratory post-hoc analysis, there was no significant association between risk of progression and the platinum-sensitivity of the patients.

In contrast, a separate phase II trial of patients (N=70) with recurrent ovarian cancer did show an impact of platinum-sensitivity on response to bevacizumab/low-dose metronomic cyclophosphamide.[19] In this study, the 6-month PFS was 56%, with 24% of patients achieving a partial response (PR). Compared with platinum-resistant patients, those with platinum-sensitive disease had significantly prolonged median PFS (*P*=.004) and median OS (*P*=.017).

These contradictory results demonstrate that for bevacizumab in particular, the question of the effect of platinum-sensitivity remains unanswered. Thus, this agent continues to be investigated in patients with both platinum-sensitive and platinum-resistant ovarian cancer. For example, the randomized GOG 213 phase III study, discussed earlier for its evaluation of secondary reductive surgery, is also significant for the fact that it is investigating the addition of bevacizumab to carboplatin/paclitaxel chemotherapy in the relapsed setting.[7] Importantly, patients randomized to the bevacizumab arm will continue to receive maintenance bevacizumab until disease progression. The OCEANS (A Study of Carboplatin and Gemcitabine Plus Bevacizumab in Patients With Ovary, Peritoneal, or Fallopian Tube Carcinoma) phase III trial randomized patients (expected, N=487) with platinum-sensitive recurrent ovarian cancer to receive either chemotherapy (carboplatin/gemcitabine) alone or the same chemotherapy backbone plus bevacizumab.[20] As in GOG 213, bevacizumab or placebo was administered

to progression. Mature results from this trial are expected soon, however, it has been released that the trial did meet its primary endpoint of PFS.

Conclusion

Despite the availability of a number of effective options for the treatment of patients with platinum-sensitive ovarian cancer, many are used without adequate data to support an advantage in OS with these interventions. The endpoints generally used in clinical trials—response rate, OS, and PFS—have a relatively linear relationship with the time of diagnosis. As each of these endpoints are improved with treatment, patients can experience longer and longer treatment-free intervals.

Platinum-sensitive ovarian cancer patients are expected to have favorable outcomes with respect to response rate, PFS, and OS when compared with patients who have either platinum-resistant or platinum-refractory disease. An abundance of studies illustrate this outcome, in particular with second-line treatment consisting of a platinum-based combination chemotherapy regimen. Future advancements are expected to revolve around these established platinum chemotherapy regimens combined with novel biologic agents.

Discussion

Deborah K. Armstrong, MD Are there any guidelines you find to be particularly helpful, especially for nonsurgical oncologists, in order to help differentiate ovarian cancer patients who are candidates for secondary cytoreductive surgery?

Robert L. Coleman, MD Chi and colleagues identified potential prognostic factors for patients who underwent a secondary cytoreductive surgery for recurrent ovarian cancer between 1987 and 2001.[21] In a multivariate analysis, factors that remained significant for patient prognosis included the disease-free interval (P=.004), the number of recurrence sites (P=.01), and residual disease (P<.001). The association of a longer disease-free interval with improved prognosis following secondary cytoreductive surgery is likely related to its link with chemosensitivity. Similarly, the extent of disease (ie, number of recurrence sites) may be considered a surrogate for the ability to achieve optimal complete surgical resection. Other factors that also may be considered include the presence of large volume ascites or signs of carcinomatosis upon imaging.

Basically, the thought is that patients with a very long treatment-free interval essentially have a disease phenotype that is very similar to a new diagnosis of ovarian cancer. Thus, because of the important impact surgery has in the initial management of ovarian cancer, there is a greater willingness to accept the risks that are associated with secondary cytoreductive surgery in this setting.

Deborah K. Armstrong, MD I think this emphasizes the point that our tools for trying to assess which patients may be completely debulked versus those patients in whom debulking will not be as successful are not very well established. They are not reliable, and they are subject to interpretation, as the definition of complete debulking may vary among experts.

Robert L. Coleman, MD Yes, you are right. One major issue in this field is the lack of good predictive models that are reproducible across different centers.

Richard T. Penson, MD This issue also leads to the point that many surgical oncologists believe that if the patient cannot be completely cytoreduced, neoadjuvant chemotherapy should be considered. This approach has been evaluated in a recent randomized, phase III trial in newly diagnosed patients, which showed that although median OS was not affected, those patients treated with neoadjuvant chemotherapy and interval debulking surgery experienced fewer complications.[22] An ongoing EORTC trial is also evaluating neoadjuvant chemotherapy in the relapsed disease setting.[6]

Deborah K. Armstrong, MD The preceding discussion focused on the use of carboplatin in platinum-based combination chemotherapy. What do you think the role is for cisplatin-based combinations in recurrent ovarian cancer?

Robert L. Coleman, MD Cisplatin/gemcitabine is an often-used combination that I particularly like. The schedule for this combination is relatively convenient for patients, as both drugs can be administered together every 2 weeks. I frequently use this combination in patients who have developed a carboplatin allergy or who have prior difficulty with thrombocytopenia.

Deborah K. Armstrong, MD Yes, I agree. I have found the cisplatin/gemcitabine combination to be fairly well tolerated, mainly due to the relatively low dose of cisplatin administered. There is also in vitro evidence suggesting that gemcitabine synergizes more effectively with cisplatin than carboplatin.[23] However, there are no randomized phase III data supporting the superiority of cisplatin/gemcitabine versus carboplatin/gemcitabine.

Deborah K. Armstrong, MD For patients who are optimally cytoreduced, is there any indication for the use of intraperitoneal therapy?

Robert L. Coleman, MD One of the issues that always surfaces regarding the use of intraperitoneal therapy is the volume of distribution, related to perfusion difficulties, intraindividual pharmacologic differences, and duration

of chemotherapy exposure. I personally do not generally advocate for the use of intraperitoneal chemotherapy, especially in recurrent disease. However, much remains to be studied regarding this treatment modality, and there is some evidence that it may be associated with improved outcomes in certain patients.

Richard T. Penson, MD We do not currently use intraperitoneal chemotherapy for our patients with recurrent ovarian cancer.

Deborah K. Armstrong, MD When discussing this option with patients, I typically emphasize that there are no randomized phase III data demonstrating a survival advantage with intraperitoneal chemotherapy in patients with recurrent ovarian cancer. I think it is important for people to make the distinction between the data available for newly diagnosed disease versus the paucity of data in recurrent disease.

Richard T. Penson, MD Are you aware of any standard use of chemosensitivity assays to help choose between paclitaxel, gemcitabine, and pegylated liposomal doxorubicin when deciding which to administer in combination with the platinum agent for second-line treatment of platinum-sensitive disease?

Robert L. Coleman, MD Commercially available assays are being used in some centers. However, several issues are centered around their use.[24,25] For example, one commercially available assay measures sensitivity against doxorubicin, not pegylated liposomal doxorubicin; any apparent difference would be very small and difficult to evaluate in a prospective clinical study. The current NCCN guidelines for ovarian cancer, although acknowledging the use of these assays, do not include a recommendation for their implementation into standard care practices.[1]

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Emerging Treatment Approaches for Platinum-Sensitive Ovarian Cancer Patients

Richard T. Penson, MD, MRCP

Emerging Concepts in Treatment

In recent years, much focus in the field of ovarian cancer has turned to new concepts in treatment and novel strategies to improve patient outcomes. Ovarian cancer is one of the initial 3 cancer types under investigation in the Cancer Genome Atlas Project, which was launched to create a comprehensive map of the genomic changes involved in cancer.[1] Recently, novel regions of loss and gain as well as novel mutations that were discovered in the initial 264 ovarian cancer specimens evaluated in this project were presented.[2] The final target accrual is 500 ovarian cancer samples. Extensive regions of gains and losses were apparent across the entire ovarian cancer genome, including large deletions on chromosomes 4, 13, 16, and 17. Recurrent amplifications and/or deletions were further mapped to individual genes, including *RB1*, *PTEN*, and *CCNE1*. Additionally, mutations in known oncogenes and tumor suppressor genes, such as *MYC*, *TP53*, and *BRCA1,* were identified.

One of the fundamental drivers of the behavior of serous ovarian cancer is p53 mutation and then failure of the DNA repair mechanisms.[3,4] This failure is essentially traced to mutations in the *BRCA1* and *BRCA2* genes, which may be exploitable and very sensitive to inhibition of poly-ADP ribose polymerase (PARP), a key molecule in DNA repair.[5] Indeed, this pathway has been successfully targeted by the PARP inhibitors olaparib (AZD-2281), iniparib (BSI-201), and veliparib (ABT-888).

A number of driving mutations have been identified in ovarian cancers; several may prove to be targetable by novel agents. One potential driving mutation has been traced to Notch signaling in ovarian cancer[6]; it appears that overactivation of the Notch signaling pathway may be related to poor prognosis, disease recurrence, and resistance to carboplatin.[7,8] The Notch ligand Jagged-1 is also upregulated in ovarian cancers,[9] and Jagged-2 has been identified as an ovarian cancer-associated antigen.[10] By dysregulating the cell cycle and suppressing BRCA2, the aurora kinase protein promotes ovarian tumorigenesis, suggesting it may also be an important driving mutation.[11] Additionally, dysregulation of the PI3K cell survival pathway may also be an important driver of endometrioid ovarian carcinoma, but it is very much more rare in this setting than in breast and endometrial cancer.

Another important question that has emerged regarding investigational therapies in ovarian cancer is whether the novel agent should be administered concurrently with standard platinum-based combination chemotherapy, or if it should be given as consolidation therapy following platinum treatment. Both of these strategies are being evaluated in the clinical trial setting.

Latest Clinical Trial Data

Some of the most exciting results from investigational agents in ovarian cancer come from PARP inhibitors. Based on their ability to augment DNA repair, PARP inhibitors are thought to have special potential in those ovarian cancer patients who possess *BRCA1* or *BRCA2* mutations. One PARP inhibitor, iniparib, is currently under investigation in 2 phase II clinical studies, in which it is being combined with carboplatin/gemcitabine in both platinum-sensitive (expected, N=41) and platinum-resistant (expected, N=48) recurrent ovarian cancer.[12,13] The primary endpoint of these studies is the objective response rate. Although recent phase III data with iniparib in metastatic triple-negative breast cancer have proved disappointing, one promising result from that clinical program is that iniparib was beneficial in patients with previously treated disease.[14] This outcome suggests that iniparib may have a greater role in the recurrent ovarian cancer setting.

Another PARP inhibitor, olaparib, has also been investigated in ovarian cancer clinical trials. In one study of patients (N=50) with *BRCA1* or *BRCA2* mutations, an overall clinical benefit of 46% was achieved.[15] Importantly, there was a significant association between the rate of clinical benefit and the platinum-free interval, and platinum-sensitive patients especially benefited from olaparib treatment. In a subsequent international, multicenter, phase II clinical trial in patients (N=57) with recurrent ovarian cancer, patients achieved an objective response rate of 13% to 33%, depending on the dosage of olaparib administered.[16] Olaparib is currently under investigation in combination with the carboplatin/paclitaxel chemotherapy combination, prior to a phase III trial.[17]

Antiangiogenic agents also hold potential for the treatment of recurrent ovarian cancer. However, it is

particularly unclear at what point during therapy patients should receive these agents: for symptomatic recurrent disease (especially ascites) or in consolidation when disease is less than 2 mm (and before activation of the angiogenic switch). This question is currently under investigation in the clinical trial setting. In addition to studies evaluating the anti-VEGF monoclonal antibody bevacizumab, studies of other VEGF-targeted agents have been promising. For example, the oral agent cediranib was found to be efficacious in a phase II trial in recurrent ovarian cancer (N=47). The rate of clinical benefit was 30%, and the median PFS was 5.2 months.[18] This agent is currently being tested in the phase III setting; the ICON6 trial is a randomized study using the same design as GOG-218, comparing carboplatin/paclitaxel with placebo, concurrent cediranib, and concurrent and single-agent maintenance cediranib in patients (expected, N=2,000) with platinum-sensitive ovarian cancer.[19]

The selective angiopoietin antagonist AMG 386 is now moving into phase III clinical trials, based on promising phase II data of its use in combination with paclitaxel in patients (N=161) with recurrent ovarian cancer. In the phase II trial, the median PFS for patients receiving the combination therapy was 5.7 to 7.2 months, compared with 4.6 months for patients who were treated with paclitaxel plus placebo.[20] In this study, which included 2 doses of AMG 386, a higher dose of AMG 386 was correlated with a trend toward prolonged PFS (*P*=.037). Further, patients receiving the highest dose of AMG 386 combined with paclitaxel achieved increased rates of objective response compared with paclitaxel/placebo, although this difference was not statistically significant (37% vs 27%). Further, 71% of patients treated with the higher AMG 386 dose achieved a confirmed CA-125 response.

Histone deacetylase (HDAC) inhibitors are another exciting class of agents being evaluated in ovarian cancer. In a phase II study of patients (N=27) with platinum-resistant or platinum-refractory disease, the HDAC inhibitor vorinostat was well tolerated but only minimally active as a single agent.[21] The combination of vorinostat with carboplatin is now under investigation in a phase I/II trial for patients (expected, N=70) with platinum-sensitive recurrent ovarian cancer.[22]

The antifolate receptor alpha antibody farletuzumab was tested in a nonrandomized exploratory phase II study in patients with platinum-sensitive recurrent ovarian cancer (N=58).[23] Patients who received the antibody plus carboplatin/taxane achieved a 70% objective response rate and a 93% clinical benefit rate. However, no objective responses were demonstrated in patients treated with single-agent farletuzumab. Importantly, 21% of the second progression-free and platinum-free intervals achieved were as long or longer than the first interval.

Importance of Quality of Life

For patients with recurrent ovarian cancer, repeated courses of chemotherapy become a fact of life. Therefore, it is essential that the clinician treating patients with recurrent ovarian cancer consider quality of life when choosing a course of therapy. For example, although the carboplatin/paclitaxel combination chemotherapy regimen is one of the most frequently used in this disease, it is associated with a relatively high rate of neuropathy and alopecia.

A novel combination involving carboplatin/pemetrexed, in which pemetrexed is given off-protocol, has shown promise in a phase II trial in patients (N=54) with recurrent ovarian cancer.[24] Although it is associated with a relatively well tolerated safety profile and thus the combination may improve quality of life for patients, this benefit is mitigated by the high cost of pemetrexed. In the future, the cost-effectiveness of novel agents will be more extensively considered, and drugs that are associated with an improved quality of life but a relatively small clinical benefit may no longer be considered for the treatment of recurrent ovarian cancer.

Conclusion

With increasing research focused on mapping the genetic basis of ovarian cancer, more and more potential rests on the identification and development of novel targeted agents. However, any efficacy or benefit associated with these novel agents must be weighed against their relative toxicity profiles as well as their ability to improve the patient's quality of life. Additionally, a greater emphasis is likely to be placed in the near future on the cost-effectiveness of these therapies. Despite these hurdles, this is an exciting time for the ovarian cancer field, with many clinical trial results eagerly awaited.

Discussion

Deborah K. Armstrong, MD Targeting the protein kinase mammalian target of rapamycin (mTOR) in endometrial cancer has elicited some very intriguing results. What is known about its potential for exploitation in ovarian cancer?

Richard T. Penson, MD There is a huge amount of interest in the interruption of the PIK3CA, PTEN, AKT, mTOR pathway. However, there has been worrying evidence about inhibition triggering positive feedback on growth and progression of tumor.[25] This has already been demonstrated with a number of other agents, and current research efforts are strongly steering investigators to combination or dual inhibition studies.

Robert L. Coleman, MD Yes, I think it is becoming clear that many ovarian tumors rely on growth signal-

ing from a number of growth factors that activate both the mTOR/PI3K kinase pathway as well as the Ras/Raf mitogen-activated protein kinase (MAPK) pathway. Blocking just one pathway may not be sufficient, and therefore dual inhibition may be necessary to achieve maximal benefit.[26,27]

Richard T. Penson, MD I recently heard language that may help to translate this point to patients, referring to "smart" tumors that use several different drivers to promote growth and survival and to rapidly change, and "dumb" tumors that rely on just one driver. The former is more difficult to turn "off," because targeting just one driver will cause the tumor to switch to one of its other drivers, while targeting the latter is simpler and can be effective with just one agent.

Deborah K. Armstrong, MD It is interesting that the phenotype of ovarian cancer is robust genetic instability. But it remains unclear what exactly drives this genetic instability.

Richard T. Penson, MD Yes, although I think that the answer is in the failure of the DNA repair machinery inherent to so many ovarian tumors. This may very well be responsible for driving the progressively unstable genome that is characteristic of ovarian cancers.

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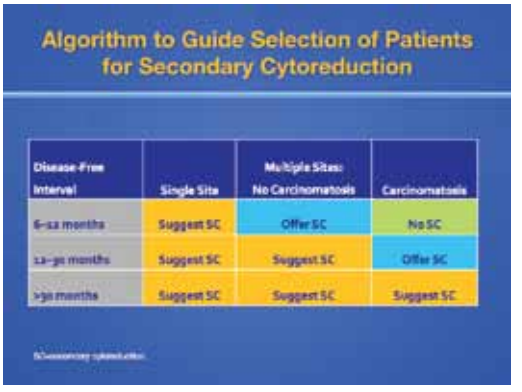

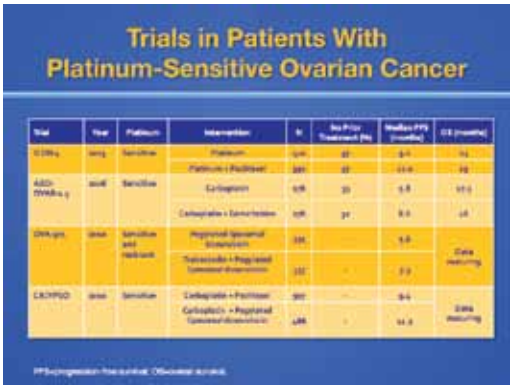

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