Rational Use of Cytotoxic Chemotherapy for Recurrent Ovarian Cancer

Joyce Liu, MD, and Ursula Matulonis, MD, Boston, Massachusetts

Abstract
Ovarian cancer remains the leading cause of death among women with gynecologic malignancies and the fifth leading cause of cancer mortality in women in the United States. Although many patients respond to first-line platinum-based therapy, most will experience disease recurrence. The role of further therapy in the setting of recurrent ovarian cancer is palliative, and large randomized phase III trials on treatment options for recurrent ovarian cancer are rare. Controversies exist as to the optimal timing and duration of treatment, and many issues regarding treatment of recurrent disease remain. (JNCCN 2006;4:947–953)

Ovarian cancer remains the leading cause of death among women with gynecologic malignancies and the fifth leading cause of cancer mortality in women in the United States.1 The most recent cancer statistics released by the American Cancer Society estimate that 20,180 new cases of ovarian cancer will be diagnosed and an estimated 15,310 deaths from this disease will occur in 2006.1 Although response to first-line platinum-based therapy in patients with advanced disease has increased to 80%,2 most patients will experience disease recurrence.3 Once ovarian cancer recurs, it is considered incurable; the cancer becomes increasingly resistant to chemotherapy and the focus of further therapy becomes palliative. This article discusses some questions that arise in treating recurrent disease and reviews the current data on chemotherapeutic options.

Key Words
Ovarian cancer, recurrent disease, cytotoxic chemotherapy

Timing of Treatment
Questions remain regarding the optimal timing to initiate salvage therapy for recurrent ovarian cancer. Patients are closely monitored after initial therapy, especially in the United States where CA 125 levels are followed up frequently. Therefore, disease recurrence is often discovered when patients are asymptomatic. Because the goal of chemotherapy in recurrent disease is palliative, some experts believe that treatment can be deferred until patients become symptomatic.4 However, an alternative perspective argues that small-volume disease may respond more optimally to treatment and, therefore, treatment should be initiated early, at recurrence, regardless of the bulk of cancer.

In addition, because response rates to chemotherapy are low, true partial or complete responses are rare. Therefore, therapy probably will not relieve symptoms. Responses to therapy that would fall under stable disease may prevent symptoms in a minimally or an imminently symptomatic patient. Currently, no data support the superiority of either approach. As less toxic chemotherapies became available, the question arises whether treatment should be continued until progression or if patients should be treated with a finite course of therapy,5 especially because data suggest that patients experiencing stable disease as a response to treatment may experience similar outcomes as those experiencing a partial response.6 This question remains unanswered.

To study the possible benefit of treatment at asymptomatic recurrence, the Gynecologic Oncology Group (GOG) is currently conducting a phase II trial (GOG 198) randomizing patients to undergo either tamoxifen or thalidomide treatment at biochemical recurrence, as determined with CA 125 levels. In Europe, a trial by the Medical Research Council (OV05) and European Organization for the Research and Treatment of Cancer (EORTC 55955) measured serial CA 125 levels in patients with clinical response to first-line platinum-based
therapy. These patients were randomized into 2 groups. In one, treatment was initiated if evidence of biochemical recurrence existed, and in the other, patients were treated with chemotherapy only if clinical recurrence was present. The results of these trials are pending but may determine whether treating patients before they become clinically symptomatic is beneficial.

**Platinum Sensitivity**

The treatment-free interval (TFI) after completion of initial therapy is an important predictor of outcome and response to further treatment. In a retrospective analysis of 72 patients initially treated with a platinum-based regimen, Markman et al. found that TFIs of 5 to 12 months, 13 to 24 months, and greater than 24 months resulted in response rates to repeat platinum-based therapy of 27%, 33%, and 59%, respectively. Patients with a TFI greater than 24 months and who underwent no intervening treatments experienced a 77% response rate and a 32% surgical complete response rate.

Given the importance of the TFI in predicting response, the GOG defined the following clinical situations: platinum-resistant disease has a TFI of less than 6 months after platinum-based therapy; in platinum-refractory disease cancer progression occurs during platinum-based therapy; and platinum-sensitive disease has a TFI of greater than 6 months after a platinum-based regimen. Notably, even in patients with initially platinum-sensitive disease at recurrence, the platinum-free interval (PFI) shortens with each subsequent treatment with platinum, eventually evolving into platinum-resistant disease with lowered overall response rates to chemotherapy.

**Treatment of Platinum-Sensitive Cancer**

**Single-Agent Therapy**

Single-agent cisplatin and carboplatin are approved by the Food and Drug Administration (FDA) for treating recurrent ovarian cancer. The response rate to these agents as single therapy in platinum-sensitive disease is up to 30%. The degree of response depends on the length of the PFI and whether the patient is primarily platinum-sensitive. Some reversal of platinum resistance is possible if the PFI is greater than 12 months. Carboplatin and cisplatin appear to have equivalent response rates in the recurrent setting to those in the up-front treatment setting, but their profiles differ.

Non-platinum single agents have also been studied in the setting of platinum-sensitive disease. Phase III trials including the use of single-agent paclitaxel, topotecan, or pegylated liposomal doxorubicin (PLD) have shown an approximately 20% to 30% response rate in patients with platinum-sensitive disease. A trial comparing single-agent paclitaxel versus a regimen of cyclophosphamide, doxorubicin, and cisplatin (CAP) showed a 45% response rate, but this was in a phase II design. The overall results suggested superiority of the CAP regimen.

Some experts have argued that the PFI in recurrent disease should be lengthened by using non-platinum single-agent therapies. This theory argues that, because PFI is linked to response, lengthening it will lead to improved outcomes. Currently, no data compare initial platinum therapy with the use of non-platinum agents to prolong the PFI. However, in trials assessing non-platinum single-agent therapies, the response rates in patients with platinum-resistant disease are approximately 10% to 15% lower than in patients with platinum-sensitive disease. This suggests that an underlying biology dictates the response to therapy and that prolonging the PFI may not alter outcomes. In selected patients, avoiding initial platinum therapy may be desirable because of concerns regarding toxicity or patient preference. In these situations, possible options for non-platinum-based therapy include pegylated liposomal doxorubicin, topotecan, or paclitaxel, but the range of choices is broad and no specific agent is superior. One phase III trial comparing PLD to topotecan in the setting of recurrent disease showed a long-term overall survival benefit associated with PLD. This trial is described in more detail in the section on “Treatment of Platinum-Resistant Disease,” but no other data support this finding. Therefore, choice of therapy in this situation should be based on ease of route of administration and avoidance of prior toxicities.

**Platinum-Based Combination Therapy**

The question of whether platinum-based combination therapy is superior to single-agent therapy in platinum-sensitive disease remains under investigation. In 2 separate retrospective analyses of patients with recurrent ovarian cancer initially treated with a platinum/paclitaxel combination therapy after presenting with platinum-sensitive recurrence, second-line...
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treatment with carboplatin and paclitaxel therapy yielded response rates of 91% and 84% and median times to progression of 9 months and 9.7 months, respectively.22,23 These results raise the question of whether platinum-based combination therapy may be superior to single-agent therapy in treating recurrent platinum-sensitive disease.

Two large randomized phase III clinical trials and a randomized phase II clinical trial have been conducted to address this issue (Table 1). The results of the phase III trials were pooled and reported together as the ICON4 (International Collaborative Ovarian Neoplasm 4)/AGO (Arbeitsgemeinschaft Gynaekologische Onkologie)-OVAR-2.2 trial.24 This trial accrued 802 patients, all of whom had platinum-sensitive recurrent ovarian cancer, between 1996 and 2002 for these 2 parallel-run trials. Eligible patients must have undergone a platinum-based regimen at initial diagnosis. In the ICON4 trial, TFI was greater than 12 months; in the AGO trial, TFI was greater than 6 months. Patients were then randomized to treatment with either single-agent platinum or the same dose of platinum with paclitaxel. Overall response rates were 66% in the group treated with platinum plus paclitaxel and 54% in the group treated with platinum (P = .06). More significantly, survival data favored the combination platinum/paclitaxel group, with a statistically significant hazard ratio of 0.82, translating into a superior median survival of 29 versus 24 months. The phase II trial, conducted by the Grupo Español de Investigación en Cáncer de Ovario (GEICO), which randomized 81 patients to treatment with carboplatin or carboplatin plus paclitaxel, suggested similar results. In this study, the response rate was 75.6% in the paclitaxel arm and 50% in the carboplatin-alone arm.25

A separate randomized phase III trial in the treatment of platinum-sensitive recurrent disease assessed the benefit of adding gemcitabine to carboplatin compared with carboplatin alone.26 Interim analysis of the data showed increased response rates with gemcitabine and carboplatin compared with carboplatin alone (response ratio, 47.2% vs. 30.9%; P = .0016). The hazard ratio for median overall survival was 0.96, but that for progression-free survival (PFS) was 0.76, with a median PFS of 8.6 months in the combined-therapy arm versus 5.8 months in the carboplatin-alone arm. Based on these findings, the FDA recently approved the use of combination gemcitabine and carboplatin for treating platinum-sensitive recurrence.

Despite the results of the ICON4, GEICO, and Gynecologic Cancer Intergroup (GCIG) trials, controversy still remains regarding the role of platinum-based combination therapy in patients with a platinum-sensitive recurrence. Criticisms of the trials include the relatively low number (40%) of patients in ICON4 who had received a taxane during their initial therapy, although 87.2% of the patients in the GEICO trial had received a prior taxane as part of initial therapy. In addition, these trials do not address the possible role of sequential therapy compared with combined therapy. Combination regimens do result in higher response rates and will likely benefit the

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symptomatic patient more rapidly. They also carry a higher rate of toxicity. In the ICON4 and GEICO trials, grade 2 to 4 neurologic toxicity of the combined platinum and paclitaxel regimen was approximately 20%, 24,25 and the GCIG study had a 78.3% incidence of grade 3 or 4 hematologic toxicity with the combined carboplatin and gemcitabine regimen. 26

An important consideration in re-treating patients with platinum is the possibility of platinum hypersensitivity reactions. In patients treated with 7 or more cycles of platinum-based therapy, the incidence of a hypersensitivity reaction is 27%. 27 This is a significant consideration in patients with recurrent ovarian cancer, and a rapid desensitization protocol has been described for treating patients with evidence of hypersensitivity. 28

### Treatment of Platinum-Resistant Disease

Patients with platinum-resistant cancer, defined as disease recurring within 6 months of the conclusion of prior platinum-based therapy, and those with platinum-refractory cancer, defined as cancer progression while on platinum therapy, carry a poor prognosis. Phase II data suggest response rates around 20% or less for single-agent therapies (Table 2), and randomized phase III trials in patients with platinum-resistant disease report response rates of 6% to 13% with a median time-to-progression of 2 to 3 months. 13,14 Scant randomized data provide guidance for therapy in platinum-resistant disease.

Because of the increased toxicities associated with combination therapy and the lack of data supporting its superiority, single-agent therapy is generally used for treating platinum-resistant disease. Drugs active in this setting include paclitaxel, 20,29,30 docetaxel, 31,32 PLD, 33-35 topotecan, 36,37 oral etoposide, 17,37 gemcitabine, 38,39 vinorelbine, 40,41 ifosfamide, 42,43 and tamoxifen or other antiestrogen therapies, including aromatase inhibitors. 44,45 No drug, however, appears to be superior.

### Taxanes

Before paclitaxel was incorporated into front-line therapy for ovarian cancer, its activity was first characterized in patients whose disease was refractory to initial platinum-based therapy. 20 After the results of GOG 111 were published, taxanes were incorporated into standard first-line therapy for ovarian cancer. For patients who have not previously received taxanes, paclitaxel can be considered second-line therapy in recurrent or platinum-resistant disease. Additional phase II studies of paclitaxel in patients with recurrent disease have shown response rates between 20% and 33%, 24,44 and dosing can be once weekly or once every 3 weeks. 24 However, a phase III trial with a 2x2 design to determine optimal dosing of paclitaxel in recurrent disease comparing high-dose versus low-dose therapy found response rates of only 15% to 20%. 46 The use of docetaxel in this setting has also been investigated, with response rates of 10% to 20% in platinum and paclitaxel-resistant disease. 31,32

### PLD

Phase II studies evaluating PLD in the setting of platinum-resistant ovarian cancer have shown a 16.9% to 25.7% response rate, with a median time-to-progression of 4.5 to 5.7 months. 13,34,49 Grade 3 or 4 hand-foot syndrome was the most significant toxicity observed in these trials, occurring in 20% to 28% of patients. The results of 2 retrospective analyses 44,45 and a phase II trial 19 with a reduced dose of PLD at 40 mg/m² given once every 28 days suggest that the reduced dosage is equally effective but carries decreased toxicity.

Two phase III trials have been conducted with PLD in the setting of recurrent ovarian cancer, one comparing PLD with paclitaxel 11 and the other comparing PLD with topotecan. 14 The trial comparing PLD with paclitaxel enrolled 214 taxane-naïve patients who experienced progression or recurrence after undergoing platinum-based therapy. Response rates between the 2 arms were statistically equivalent: 17.8% for the PLD arm and 22.4% for the paclitaxel arm. Median PFS was 21.7 weeks and 22.4 weeks, and overall survival was 43.7 weeks and 56.1 weeks in the PLD and paclitaxel arms, respectively.

Interestingly, although overall response rates were equivalent in the phase III study comparing PLD with topotecan in recurrent disease (19.7% for PLD vs. 17.0% for topotecan), PFS (28.9 weeks vs. 23.3 weeks, respectively) and overall survival (108 weeks vs. 71.1 weeks) for the subgroup of patients with platinum-sensitive disease favored PLD in a statistically significant manner. Overall survival for the whole group undergoing longer follow-up favored PLD over topotecan (hazard ratio, 0.82; P = .05), but no statistically significant difference occurred in overall survival for patients with platinum-resistant disease. 21 Bone marrow suppression and dose-adjustments were more frequent in the topotecan arm.
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**Topotecan**

Phase II clinical trials with topotecan administered parenterally as a 5-day infusion in recurrent ovarian cancer have yielded response rates between 14% and 27%, depending on the status of platinum resistance.\(^{19,36,52}\) 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.\(^{19}\) The major toxicity of topotecan has been hematologic, with grade 3 or 4 toxicity occurring in up to 95% of patients.\(^{19,52}\) Alternative dosing regimens from the standard 1.5 mg/m\(^2\) have been compared, and a lower dose of 1.0 mg/m\(^2\)/d for 5 days has been reported to have similar phase II response rates and decreased toxicity, as does weekly dosing.\(^{35,54}\)

Phase III studies have also compared topotecan with paclitaxel and PLD in recurrent disease.\(^{13,14}\) The trial involving PLD was discussed earlier. In the phase III trial comparing topotecan with paclitaxel in patients experiencing recurrent disease after undergoing prior platinum-based therapy, overall response rates were 20.5% and 13.2%, respectively (\(P = .138\)), and response rates in platinum-resistant disease were 13.3% and 6.7% (\(P = .303\)), respectively. The median time to progression favored topotecan at 23 weeks versus 14 weeks (\(P = .002\)).

**Other Agents and Modalities**

Many additional agents have comparable response rates in treating ovarian cancer. Results of phase II trials with these agents are summarized in Table 2. Another agent being investigated for the treatment of recurrent ovarian cancer is bevacizumab. Response rates for bevacizumab approach 16% in both platinum-sensitive and platinum-resistant ovarian cancer.\(^{35,50}\) Recently, an overall response rate of 16% was reported in a patient population whose disease was platinum-refractory and had progressed through treatment with either topotecan or PLD, but the trial closed early because of a higher-than-expected rate (11%) of gastrointestinal perforations.

In addition to intravenous-based chemotherapy, intraperitoneal (IP) platinum-based chemotherapy can also be considered for selected patients with highly platinum-sensitive disease. Studies of IP therapy in recurrent disease have shown that response rates are low in patients with bulky disease.\(^{57}\) Therefore, this modality should only be considered in selected patients who have very platinum-sensitive cancer, are motivated to undergo IP chemotherapy, have no evidence of extra-abdominal cancer, and undergo interval surgery after recurrence, resulting in optimal debulking (1 cm or less of residual cancer). A more complete discussion of IP therapy for recurrent ovarian cancer is beyond the scope of this article.

**Summary**

The National Comprehensive Cancer Network (NCCN) has published guidelines on the treatment of ovarian cancer, including recurrent disease.\(^{58}\) Overall, experts must regard recurrent ovarian cancer as 2 separate entities: platinum-sensitive disease and platinum-resistant disease. In patients for whom systemic therapy is an option, chemotherapy is indicated for either preventing or treating symptoms of ovarian cancer. Some experts believe that patients with platinum-sensitive recurrent ovarian cancer who have longer PFIs may be considered for platinum-taxane regimens unless previous toxicities preclude their use. Otherwise, for the asymptomatic or minimally asymptomatic patient, single-agent therapy should be used, depending on the degree of platinum sensitivity, previous toxicities, route of administration, and avoidance of certain toxicities as requested by the patient.

Response rates of chemotherapy drugs are lower in patients with platinum-resistant cancer than in those with platinum-sensitive cancer. No drug appears to be
superior for treating platinum-resistant ovarian cancer. More recently, studies with bevacizumab have shown activity in the platinum-resistant setting, both in combination with other cytotoxic agents and as a single-agent therapy, but with significant complications including gastrointestinal perforation. The timing of therapy also remains controversial, and no data currently support the optimal timing. For platinum-sensitive disease, although experts have discussed using non-platinum agents to extend the PFI, no data support this practice.

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