

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: James L. Abbruzzese, MD

New Agents and New Formulations for the Treatment of Ovarian Cancer

Paul Sabbatini, MD
Assistant Attending Physician
Gynecologic Medical Oncology Service
Memorial Sloan-Kettering Cancer Center

H&O What are the current outcomes for patients with ovarian cancer?

PS The outcomes for patients with ovarian cancer have definitely improved in the last 30 years. The overall survival in 1975 was approximately 1 year; more recently, a clinical trial for patients with optimally debulked disease showed a median overall survival in excess of 5 years. However, looking at this data another way, only about 30% of patients do not relapse at some point. Therefore, the majority face recurrent disease with continued and often repeated treatment. Progress is undeniable, but there is a clear need to develop other strategies to further delay or ultimately prevent recurrence.

H&O What are the most common agents or regimens associated with the longer survival times?

PS The impact of aggressive surgical debulking and the introduction of taxane- and platinum-based therapy have been responsible for the initial gains. We had reached a plateau in overall survival with standard treatment until recent data has again caused a reevaluation of direct intraperitoneal (IP) delivery of chemotherapy.

There are now 3 randomized trials supporting the benefit associated with IP treatment. The first predated paclitaxel and carboplatin use and simply asked the question of whether intravenous (IV) or IP administration of cisplatin was better, showing an advantage for the latter (median overall survival 49 vs 41 months, $P=.02$).¹ This study has been criticized because it does not contain paclitaxel, and thus does not reflect contemporary

treatment. The second study included paclitaxel, but the experimental arm not only included IP delivery of cisplatin, but also added high-dose IV carboplatin for several cycles.² This study, while also showing an advantage for the IP-containing experimental arm (overall survival 52 vs 63 months, $P=.05$), was criticized because more than 1 variable was changed and the benefit could not be directly attributed to IP therapy. The third and only well-designed study has been reported only in abstract form to date and compares IV paclitaxel and cisplatin with IV and IP paclitaxel and IP cisplatin. The relative risk of recurrence was 0.73 favoring the IP group.³ Final results will be available soon and will make a strong case for accepting IP treatment as part of the initial therapy for patients with optimally debulked ovarian cancer.

H&O Is IP delivery more effective because a higher percentage of the drug is reaching the site of the cancer?

PS Different theories exist to explain the efficacy of IP delivery. One theory attributes its effectiveness to the high concentration of drug reaching the tumor, but it is noted that other systemic high-dose approaches have not been more effective than standard doses. Another possible explanation is that its efficacy is due to the longer exposure time associated with this administration method, coupled with the direct delivery of drug to the tumor site.

H&O What are the side effects associated with IP treatment and will studies in the future address ways to decrease side effects?

PS Electrolyte imbalances or metabolic complications associated with cisplatin have been reported. Neuropathy is another notable side effect. We can expect studies that employ alternate drugs (eg, substituting carboplatin for cisplatin at the IP port), modify the dose of drugs (eg, lowering the cisplatin dose), or even revise the schedule (eg, removing the IP paclitaxel dose from day 8). IP delivery of at least part of primary therapy has clearly shown an advantage in outcome, so the next question is to find a way to make the treatment less toxic.

H&O What are some of the new agents?

PS There has been a recent focus on anti-vascular endothelial growth factor (VEGF) strategies in a variety of tumors. Two recent studies reported in abstract form showed the activity of bevacizumab (Avastin, Genentech) in patients with ovarian cancer. A phase II trial evaluating bevacizumab at 15 mg/kg every 3 weeks as second- or third-line therapy showed a single-agent response rate of 17%, with a median progression-free interval of approximately 10 months.⁴ A second phase II study evaluated bevacizumab in conjunction with oral cyclophosphamide, showing partial responses in 28% of patients and stable disease in an additional 59%, with a median progression-free interval of 5.8 months (95% confidence interval [CI], 3.8–8.1 months).⁵ At 6 months, approximately 57% of patients remained progression-free. Recently, an advanced ovarian cancer trial evaluating bevacizumab in refractory ovarian cancer patients with measurable disease was halted due to an excess in bowel perforation, which is a known side effect. The Gynecology Oncology Group (GOG) currently has an ongoing randomized study evaluating bevacizumab in addition to paclitaxel and carboplatin for patients who are suboptimally debulked. Other studies with anti-VEGF strategies such as the oral agent PTK787/ZK222584 (Novartis) and VEGF-TRAP (Regeneron) are currently underway to define both toxicity and efficacy, and there is much interest in defining the role of these agents in ovarian cancer treatment.

H&O Can you briefly explain how angiogenesis inhibition applies in ovarian cancer?

PS There is clear evidence that patients with increased levels of VEGF have a worse prognosis in ovarian cancer compared to patients with lower levels of VEGF. This finding makes the targeting of VEGF particularly attractive for patients with ovarian cancer. Secondly, ascites, which is a characteristic of ovarian cancer, is generally a VEGF-rich fluid. Responders to anti-VEGF therapy tend to have rapid resolution of ascites if the therapy is working.

H&O Is bowel perforation, which is also associated with bevacizumab therapy in patients with colorectal cancer, an effect of the agent regardless of the disease being treated? Are there other agents that do not carry similar risks?

PS The absolute incidence of bowel perforation in ovarian cancer is still being assessed. It is too soon to say from published information whether it is related to extent of disease, amount of disease on bowel, number of prior regimens, or other factors. Other anti-VEGF agents under evaluation may have different toxicity profiles.

H&O What is the efficacy of erlotinib in ovarian cancer?

PS Schilder and colleagues reported on the GOG experience with gefitinib (Iressa, AstraZeneca), which is in the same class of drugs as erlotinib (Tarceva, Genentech/OSI).⁶ This study showed minimal single-agent activity in unscreened patients with regard to endothelial growth factor mutation or overexpression.

Research is underway examining cetuximab (Erbix, Bristol-Meyers Squibb/ImClone) and erlotinib in conjunction with chemotherapy, based on previous data suggesting that while single-agent activity is minimal, combination therapy may have synergistic activity.

H&O Are there other agents being considered for patients with ovarian cancer?

PS A recent study by Sessa and coworkers reported a 43% response rate for trabectedin (Yondelis, PharMar) for patients with platinum-sensitive ovarian cancer. This response rate is similar to that reported in studies with other nonplatinum agents, and an obvious next step would be to evaluate this agent in conjunction with platinum if the toxicity profile will allow; these studies are underway.⁷

H&O What about oregovomab?

PS Oregovomab (OvaRex, Unither) is an interesting monoclonal antibody. It was examined recently by Berek and colleagues in a randomized placebo-controlled study of patients in first clinical remission. While the intent-to-treat analysis showed no benefit, a subgroup of patients they called the “successful frontline population” had an increase in time-to-relapse from 10.8 to 24 months (hazard ratio 0.543; 95% CI, 0.287–1.025) among those receiving antibody.⁸ This agent is now being tested in that subset.

The overall approach of immune-directed therapies to include vaccine and monoclonal antibodies remains promising, and many more studies will hopefully be available in the upcoming months for patient participation.

H&O Is ovarian cancer uniquely suited for therapies strictly aimed at treatment during remission to prevent recurrence?

PS Absolutely. The natural history of ovarian cancer is one of relapse and remission. Clinical trials have traditionally evaluated new agents as a part of primary therapy or for recurrence, but newer approaches with acceptable side effect profiles are well suited for evaluation in the remission setting.

H&O How are patients with a rising CA125 level but no radiographic evidence of recurrence treated?

PS In the situation of a patient with a rising level of CA125 who does not yet have relapse observable by computed tomography, no data have suggested that “early” chemotherapy is better than “later.” The goal of treatment is to intervene before there are significant symptoms, but not so soon as to add the toxicity associated with treatment to an otherwise asymptomatic patient. Physicians often use tamoxifen in this situation, and the GOG is conducting a randomized trial of tamoxifen versus thalidomide (Thalomid, Celgene) for this patient group. A planned multicenter trial chaired by Dr. Seiden at the Dana Farber Cancer Institute will examine HYB2055 (Imoxine, Hybridon) and include patients with a rising CA125 level as the only evidence for disease. There is much interest in evaluating a variety of immune-based or other nontoxic treatments in this patient group with the goal of delaying radiographic recurrence.

H&O Is research under way to identify which patients in remission are more likely to relapse?

PS This is a very important area of research. Since rates of relapse are high in ovarian cancer, there is a great need to discover which patients in remission are most likely to relapse and stratify them accordingly as new agents are tested. Researchers are now examining the nadir CA125 level with regard to its ability to predict relapse even with changes in the normal range. Others have shown that VEGF levels correlate with outcome. Springett and coauthors published an article in the October 2005 issue of *Cancer Research* on lysophosphatidic acid acyltransferase (LPAAT)- β as another marker for prognosis.⁹ In the future, as clinicians start thinking about testing remission strategies, it is important to know the natural history of

this population and how to better define it. It is necessary to know what signals to watch for in order to move a strategy from a phase II trial to a large randomized phase III trial. It is my hope that the focus on consolidation strategies will continue to intensify as new nontoxic approaches are developed.

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