ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: Clifford Hudis, MD

Update on Treatment Options for Newly Diagnosed Ovarian Cancer

Deborah Armstrong, MD
Associate Professor of Oncology
Department of Gynecology and Obstetrics
Sidney Kimmel Comprehensive Cancer Center
at Johns Hopkins
Baltimore, Maryland

H&O What are some of the main risk factors for ovarian cancer?

DA Within the ovary there are 3 cell types that can give rise to cancer. The first type is the germ cell. Germ cell cancers of the ovary are highly analogous to testicular cancers in men. They tend to occur in young people in their teens and 20s, and even in the setting of advanced disease, they are highly curable. The second type of cell is a stromal cell, and this is frequently the ovarian cell type that gives rise to hormones from the ovaries and is sometimes associated with excess hormone production. Stromal cell cancers are not very common. The most common cancer and the one that is most recognized is the cancer that arises from the ovarian epithelial cell; ovarian epithelial cancer originates from the surface of the epithelium overlying the ovary. From a clinical perspective, what we call ovarian cancer is really one of 3 cancers: ovarian epithelial cancer, fallopian tube cancer, and primary peritoneal cancer. All 3 types have the same risk factors, though there are some subtle differences.

The risk factors for ovarian cancers vary. In sporadic ovarian cancer—the most common type of ovarian cancer—one of the risk factors is the number of lifetime ovulations. The process of injury and repair, where the surface of the ovary ruptures and the ovum is extruded and passes through the fallopian tubes, can be associated with initiating events for cancer formation. Some of the evidence in support of this risk factor include starting menarche (ie, starting ovulation) at a younger age and going through menopause at a later age. Conversely, an increased number of pregnancies, breast feeding, and the use of oral contraceptives decrease the risk of ovarian cancer. The number of lifetime ovulations is a weak risk factor—as evidenced by the number of women with children who are diagnosed with ovarian cancer—but is fairly consistent across multiple studies.

Genetic predisposition is another risk factor for ovarian cancer. Women who have 1 of the 2 BRCA genes (BRCA1 or BRCA2) are at an increased risk of ovarian cancer, and the fold elevation for risk is higher than it is for breast cancer. Women with a BRCA mutation have a 10–40% risk of ovarian cancer, whereas the incidence of ovarian cancer in the general population is 1–2%.

H&O What is the current state of screening methods for ovarian cancer?

DA One of the main problems we face is that except for women with known BRCA mutations, we do not know what the absolute risk is for ovarian cancer in most women. Unfortunately, we do not know the true etiology of ovarian cancer. We do not have the equivalent of the human papillomavirus in cervical cancer or tobacco and cigarette smoking in lung cancer.

Another major problem seen with ovarian cancer is that most women are diagnosed with advanced disease (75–80% have stage III or IV disease at diagnosis). Patients diagnosed with stage I or stage II disease have excellent survival, but these patients only comprise approximately 20–25% of all patients. Thus, finding a way to diagnose patients in earlier stages would help prevent advanced cancer and would lead to increased survival, as the majority of women diagnosed at earlier stages survive their disease. Because of the advanced stage at diagnosis seen in most women, there has been a lot of interest in developing screening modalities for ovarian cancer.

Because only 1–2% of the female population is at risk for ovarian cancer, any screening technique that is being developed has to be highly sensitive and highly specific in order to avoid false positives (to reduce unnecessary surgeries) and false negatives (so that we do not miss ovarian cancer). Interestingly, the screening studies that were done in the late 1990s and the early part of this decade that focused on high-risk women with a BRCA mutation were pretty disappointing.

There have been recent studies analyzing possible screening methods; data presented at this year's American Society of Clinical Oncology (ASCO) meeting by Dr. Karen Liu and the data published by Drs. Usha Menon and Ian Jacobs in Great Britain looked at the patient population of women without a family history who were postmenopausal (≥50 years); neither of the 2 studies included women who were high risk or those who had a known BRCA mutation. The studies examined screening modalities, including measurement of CA125 by a blood test (annually) and referral to an ultrasound or sonogram based on the difference in CA125 from previous measurements. In Dr. Karen Liu's study, 8 surgeries were performed, which found 3 cases of invasive ovarian cancer (all stage I or II). Two other surgeries were performed for low malignant potential tumors, and 3 surgeries were done for nonovarian cancer conditions. The investigators found that there was no ovarian cancer development in women who did not have surgery. Studies such as these are beginning to utilize the risk of ovarian cancer algorithm (ROCA), which looks at the changes in CA125 over time for an individual woman. If the value changes, the patient is either referred to get an ultrasound or to see a gynecologic oncologist. We are still in the early stages of using ROCA, but in the future we hope to use this algorithm or a similar strategy for screening for ovarian cancer. If the Great Britain study shows a survival benefit for this type of screening, we will then move forward with broader population testing of these screening strategies.

Currently, outside of clinical trials, there is no standard screening for women. For those women with a BRCA mutation, we recommend an internal examination, a pelvic exam by a gynecologic cancer specialist, CA125 screening, and a transvaginal ultrasound. However, we do not have any data to suggest that any of these recommendations are beneficial, and that is why the general recommendation for these women is to have a salpingo-oophorectomy after child bearing.

H&O How does disease stage influence treatment options?

DA Some stage I patients who are diagnosed with stage IA or IB disease that is well-differentiated have a greater than 90% 5-year disease-free survival rate and thus receive no benefit from chemotherapy. In situations where a patient has stage I disease that involves the surface of the ovary or there are positive washings (ie, cancer cells floating in the abdomen), or if the cancer ruptures, the patient is at risk for having residual cancer cells grow and cause a recurrence. Stage IA and IB patients who have poorly differentiated tumors (ie, high grade) receive chemotherapy. Stage II patients by definition have had some disease spread outside the ovaries, so they all receive chemotherapy. It is pretty rare for a newly diagnosed patient with ovarian cancer not to receive chemotherapy.

H&O What is the typical management of newly diagnosed ovarian cancer?

DA In addition to chemotherapy, debulking surgery is also part of the standard treatment recommendation for ovarian cancer. The use of debulking even in the setting of fairly extensive disease that is outside the organ of origin is unique to ovarian cancer. There are not many solid tumors in which this is done as part of routine care.

There are numerous retrospective data that demonstrate that one of the main prognostic factors in ovarian cancer is the volume of disease left after surgery, and the less disease there is, the better the survival. A potential reason for this correlation between survival and lower volume of disease is related to the unique pattern of spread of ovarian cancer. Just like any other tumor, it can spread hematogenously (via the blood stream) or can spread by the nodal system. When this occurs, the tumor has a way to get oxygen and nutrients from the lymphatic channels or the blood stream. However, most of the disease seen in ovarian cancer is not from hematogenous or lymphatic dissemination, but from the cancer cells shedding from the surface of the ovary. These cells circulate throughout the abdominal peritoneal cavity and implant on peritoneal surfaces. To be able to grow, the cells must be able to develop a blood supply. This may explain why ovarian cancer is highly responsive to vascular endothelial growth factor (VEGF)-targeted therapies. Access to the bulk of the disease, which is in the peritoneal cavity, is possible through surgery.

For 90–95% of patients, debulking surgery is performed prior to chemotherapy, with the goal of producing no visible residual disease. Part of the problem is that it is not always possible to predict in advance who will be able to have optimal surgical debulking. There are some patients (10–15%) who are not fit enough to undergo surgical debulking either due to medical problems or comorbidities, or because the location and volume of disease will not allow for a good surgical debulking. In such cases, chemotherapy can be administered first. Cer-

tainly, surgery for ovarian cancer can be made a lot easier if chemotherapy is given first, but in the United States, our approach is to perform surgical debulking and then administer chemotherapy. We feel very strongly that all patients deserve to see a gynecologic oncology specialist to assess for potential surgery before undergoing chemotherapy. There are some gynecologic oncologists who believe that a patient will be better served by getting chemotherapy prior to surgery, but it should be a gynecologic oncologist who makes that decision.

A recently published study from our British colleagues in the *New England Journal of Medicine* compared administration of neoadjuvant chemotherapy followed by interval surgery versus surgery followed by chemotherapy. The results showed no difference in survival between the 2 arms; however, the overall survival was inferior to that in almost all the studies that have been conducted in this setting, even in patients with highly advanced ovarian cancer.

H&O What are the main challenges with treating newly diagnosed patients?

DA The first main challenge is the access to good surgery for the first surgery. There are very clear data that demonstrate that unless a hospital and the surgeon at the hospital perform at least 10 ovarian cancer surgeries per year, they will not do as good of a job as a gynecologic oncologist who specializes in such surgeries. Unfortunately, only about half of patients in the United States have their surgery performed by a gynecologic cancer specialist. Commonly, a patient will go to a gynecologist who will perform the surgery or the patient will go to the emergency room with abdominal pain and a general surgeon will perform the surgery. Our goal is to advocate for patients to always see a gynecologic cancer specialist prior to surgery.

H&O Can you discuss some ongoing research in newly diagnosed patients?

DA In ovarian cancer, platinum drugs are the backbone of chemotherapy treatment. We have looked at platinum drugs in combination with other agents and have determined that the combination of a platinum with a taxane (usually paclitaxel) is typically the combination that produces the highest response. For many patients, the majority of their disease is in the peritoneal cavity, and we have the ability to administer chemotherapy into the peritoneal cavity. We have conducted 3 large studies in the United States over the past few decades that looked at the use of intraperitoneal (IP) therapy. All 3 studies showed a survival benefit for patients who received IP therapy. The biggest concern with IP therapy is that it can be difficult to administer; it requires a different technology and experience in not just treating ovarian cancer patients but treating ovarian cancer patients with IP therapy; it also can be toxic. There is currently an ongoing nationwide study of the Gynecologic Oncology Group, GOG 252, that is using a modification of the IP cisplatin regimen in one arm, IP carboplatin in the second arm, and weekly intravenous paclitaxel in the third arm.

Another agent being studied in ovarian cancer is bevacizumab (Avastin, Genentech). At this year's ASCO meeting, Dr. Robert Burger presented data from GOG 218 that examined the use of bevacizumab in combination with chemotherapy in ovarian cancer. The study had 3 arms: chemotherapy only, chemotherapy plus bevacizumab, and chemotherapy plus bevacizumab followed by bevacizumab maintenance. The findings showed a statistically significant difference in the progression-free survival (PFS) rate between the first and third arm, but no difference in PFS between the first and second arm, suggesting that just using bevacizumab with chemotherapy does not improve outcome, but using bevacizumab with and after chemotherapy as maintenance results in an improvement in PFS. Some of the controversy surrounding this study is that with approximately 25% of patients in any of the arms having died, there is no survival benefit shown. Toxicities have also been reported with bevacizumab, including a slight increase in the gastrointestinal perforation rate (1%), significant hypertension rates (20–25%), clotting problems, and some proteinurea. In my opinion, the use of bevacizumab with chemotherapy remains an unproven benefit and is still controversial. At this time it is difficult to justify routinely adding a drug as costly as bevacizumab to initial chemotherapy if it does not improve survival.

There are several other agents that look promising, in particular poly(ADP-ribose) polymerase (PARP) inhibitors, which have been studied in recurrent disease. In patients with BRCA-associated ovarian cancer, PARP inhibitors have been shown to have a fairly significant response rate when given alone. At this year's ASCO meeting, Dr. Karen Gelmon from the Breast Cancer Tumor Group at the British Columbia Cancer Agency presented data from a study of olaparib (AstraZeneca), a PARP inhibitor. One of the arms in the study consisted of ovarian cancer patients who did not have a BRCA mutation; these patients had approximately a 24% response rate, which suggests that the use of PARP inhibitors not just in BRCA mutation–carrier ovarian cancer, but also in sporadic ovarian cancer, might prove to be beneficial. There is an ongoing phase I study being done by GOG that is looking at the PARP inhibitor ABT-888 (Abbott) combined with initial chemotherapy and bevacizumab in patients with ovarian cancer. The objectives of this study

are to determine the safety of these drugs in combination and the best way to use them.

There is also a family of agents that target the folate receptor alpha (FRα) that is being studied in ovarian cancer. Folate is a B vitamin that gets into cells by 1 of 2 mechanisms: through the FRα or through the reduced folate carrier (RFC). The RFC is responsible for most of the folate getting into cells, but FRα has been found to be overexpressed in a number of cancers. The highest levels of expression in solid tumors are in ovarian cancer; over 90% of ovarian tumor specimens overexpress FRα. This suggests that it may be a good target for therapy. Another study reported at the ASCO meeting this year evaluated the use of FRα targeting along with a chemotherapeutic agent. Patients in the study received pegylated liposomal doxorubicin with or without EC145 (Endocyte). EC145 is a FRα antibody linked to a vinca alkyloid. The addition of EC145 resulted in a significant increase in the response rate and PFS, suggesting significant activity. Farletuzumab (Morphotek, Eisai) is another drug being tested that targets the folate receptor. Farletuzumab is an antibody to the FRα, and in our early studies it produced an improved outcome when used with chemotherapy. The final report of a phase II study analyzing this combination was presented at this year's ASCO meeting. There are also ongoing, larger randomized studies looking at farletuzumab in ovarian cancer.

H&O What are the main areas of research?

DA Part of the reason there is an interest in studying bevacizumab in newly diagnosed ovarian cancer patients is because it has a remarkable response rate when used alone. Bevacizumab is being used primarily in combination with chemotherapy in colorectal cancer, lung cancer, and, up until recently, breast cancer. It does not work when given as a single agent in these diseases, but appears to make chemotherapy work better. However, in ovarian cancer, single-agent bevacizumab is effective, possibly due to the fact that this disease is very dependent on developing new vasculature and may be one of the most VEGF-dependent cancers. In addition to bevacizumab, there are a number of other antiangiogenesis-targeting agents being studied, including some oral agents and tyrosine kinase inhibitors.

There was a study presented by Dr. Beth Karlan at the ASCO meeting that looked at AMG 386 (Amgen), a peptibody that targets the angiopoietin axis. Some type of angiogenesis targeting, such as with these peptibodies, may have a significant role in ovarian cancer. Given the activity of bevacizumab, there is a lot of ongoing research looking at these families of agents in the second-line setting as well as in newly diagnosed patients as consolidation treatment.

At present, the main focus of research in ovarian cancer is targeting vasculature and VEGF and the PARP inhibitors. The other avenue of research is trying to predict which patients will respond to these new agents. Although bevacizumab has a great response rate in ovarian cancer, the majority of patients will not respond to it, and if we can figure out based on tumor characteristics who will respond and who will not, the whole biomarker field will potentially allow us to provide these agents to people who have a higher likelihood of response. This is going to be true not just of VEGF-targeted therapies and PARP inhibitors but in targeted therapies in general, and not just in ovarian cancer but in other cancers as well.

Suggested Readings

Gelmon KA, Hirte HW, Robidoux A, et al. Can we define tumors that will respond to PARP inhibitors? A phase II correlative study of olaparib in advanced serous ovarian cancer and triple-negative breast cancer. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2010;28(15s):Abstract 3002.

Burger RA, Brady MF, Bookman MA, et al. Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC): a Gynecologic Oncology Group study. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2010;28(15s):Abstract LBA1.

White AJ, Coleman RL, Armstrong DK, et al. Efficacy and safety of farletuzumab, a humanized monoclonal antibody to folate receptor alpha, in platinum-sensitive relapsed ovarian cancer subjects: final data from a multicenter phase II study. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2010;28(15s):Abstract 5001.

Vergote I, Tropé CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med.* 2010;363:943-953.