

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: James L. Abbruzzese, MD

Second-line Therapy for Ovarian Cancer

Maurie Markman, MD
Vice President for Clinical Research
The University of Texas
M. D. Anderson Cancer Center
Houston, Tex.

H&O What challenges does ovarian cancer pose in the second-line setting?

MM The majority of patients with ovarian cancer, even if they respond to first-line therapy, eventually experience disease recurrence. Therefore, second-line therapy is relevant to most patients. The paradigm of second-line therapy, however, differs from that of first-line therapy. First-line therapy has curative intent—to rid the patient of clinically evident disease for the remainder of her life—but there is no evidence that second-line therapy can cure patients with ovarian cancer. The goals, therefore, are to prolong survival; to improve quality of life; and to prevent, delay, and/or treat symptoms. Clinicians must understand that, based on the available evidence, the disease cannot be eliminated after relapse. Clinicians must also be aware of the potential toxicities of second-line therapy because a patient may have already experienced toxicities resulting from first-line therapy. Even if a patient has not experienced toxicities, there could be a cumulative or additive toxic effect in the second-line setting. For example, one of the problems associated with primary chemotherapy of ovarian cancer, which is platinum- and taxane-based, is neuropathy that can be quite symptomatic in some patients. If a patient has experienced neuropathy due to first-line therapy that has subsequently resolved, it can return with re-treatment. Even if a patient has not experienced neuropathy, there can still be sub-clinical effects caused by these agents, which can lead to neuropathy occurring in the second-line setting. Finally, a major challenge is the paucity of data at present defining the optimal treatment in the second-line setting.

H&O What approaches are used in the second-line setting?

MM Patients can be divided into two general categories, those who have not responded to platinum-based therapy or recurred within 6 months of the completion of their primary chemotherapy regimen and women who have responded and recurred more than 6 months after their last platinum treatment. It should be clearly understood that the likelihood of responding a second time to a platinum-based program is a continuum, with longer platinum-free intervals associated with a greater statistical likelihood of achieving an objective response. In general, based on existing evidence-based, phase III trial data, if a patient can tolerate such treatment, it is rational to recommend combination therapy with either carboplatin plus paclitaxel or carboplatin with gemcitabine (Gemzar, Lilly) as the initial choice for management second-line chemotherapy in patients with recurrent potentially platinum-sensitive (defined above) ovarian cancer. Randomized trials that compared these combinations to single-agent carboplatin revealed an improvement in survival outcomes (“progression-free” for carboplatin plus gemcitabine; “progression-free and overall” for carboplatin plus paclitaxel). Ongoing trials are investigating other combinations, such as carboplatin and liposomal doxorubicin (Doxil, Ortho Biotech), but definitive data are still needed. Again, it is critical to note that although combination regimens have improved outcome in the recurrent setting, the disease will recur. Additionally, there are some patients in whom the use of combination therapy may be relatively contraindicated (eg, significant comorbidity; substantial bone marrow suppression with primary chemotherapy). In these patients single-agent carboplatin is a reasonable option, followed at the time of progression or as

a planned sequential drug delivery strategy, by other single agents (eg, gemcitabine, paclitaxel, liposomal doxorubicin, etc.).

If a patient experiences recurrence quickly (ie, <6 months), or if the individual has initially responded to second-line combination therapies but nevertheless after some time develops a recurrence, there are as many as a dozen options currently available for treatment. However, it is important to recognize that in this platinum-resistant setting there is currently no evidence for the superiority of any particular strategy compared to a number of alternative options. Most ovarian cancer patients who are found to be platinum-resistant after primary therapy, or are defined as being potentially platinum-sensitive but do not respond to a second-line platinum program or subsequently recur (after a secondary response to a platinum regimen), are treated sequentially with multiple single-agent regimens. There is no evidence that combination regimens in the platinum-resistant setting are superior to single agents. Further, combination regimens are likely to be associated with greater toxicity and also decrease the number of available monotherapies for later use. The clinician's decision regarding which drug to administer and when to administer it to a platinum-resistant patient will be individualized based upon previously experienced toxicities, patient preference, comorbidities, the availability of (and interest in) clinical trials, insurance reimbursement, patient travel distance to the clinic, and other individual factors. For example, weekly therapy may not be as reasonable as therapy given once every 3 or 4 weeks for some patients depending on their individual living situations; a completely ambulatory patient will have different considerations from a patient who must rely on family members for mobility. In the absence of data demonstrating an efficacy advantage for any particular therapy in the platinum-resistant setting, individualized and quality of life–based concerns help dictate the choice of therapy even more than they might in other malignancies wherein a clear survival advantage exists for a given therapy.

H&O What research is currently ongoing in the second-line setting?

MM There are new agents under investigation in phase I and II studies for the second-line therapy of ovarian cancer. Past phase III trials have not shown new agents to confer a survival advantage over traditional therapies. For example, canfosfamide, a novel glutathione analog prodrug activated by glutathione S-transferase P1-1, was investigated in a randomized, phase III trial in the third-line setting versus either liposomal doxorubicin or topotecan (depending on what regimen the patient had received as second-line therapy). This trial showed inferior survival for the patients who received the experimental therapy. Therefore, clinicians must never assume that therapies in the second-, third-, or fourth-line settings are interchangeable; moreover, novel therapies should not be considered ipso facto superior to traditional therapies.

There are many interesting therapies being developed, such as antiangiogenic agents, which appear to have activity in resistant/recurrent ovarian cancer. There is no evidence yet that these agents are more effective than chemotherapy, but there is a potential that a novel mechanism of action could enable a response when resistance to chemotherapy occurs. These agents may also have different, and favorable, toxicity profiles. There exists the possibility of combining novel, targeted agents with standard chemotherapy. Clinical trials are needed to understand these agents better. At present, no evidence exists that shows combination therapy to be superior to monotherapy in the resistant setting.

Suggested Readings

- Kaye SB. New drugs for ovarian cancer. *Clin Adv Hematol Oncol*. 2008;6:91-93.
- Markman M. Pharmaceutical management of ovarian cancer: current status. *Drugs*. 2008;68:771-789.
- Vergote I, Finkler N, del Campo J, et al. Single agent, canfosfamide (C, TLK286) vs pegylated liposomal doxorubicin (D) or topotecan (T) in 3rd-line treatment of platinum (P) refractory or resistant ovarian cancer (OC): Phase 3 study results. *J Clin Oncol*. 2007;25(18S): Abstract LBA 5528.
- Vermorken JB. Second-line randomized trials in epithelial ovarian cancer. *Int J Gynecol Cancer*. 2008;18(suppl 1):59-66.