Commentary (Muggia/Blank): Modern Management of Recurrent Ovarian Carcinoma

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The Michener/Belinson article deals not so much with what is new in the treatment of ovarian cancer, but with the changing management paradigm. The authors correctly point out that one cannot expect to offer curative options in ovarian cancer patients who recur. Consequently, in planning therapy, the focus should be on the ability to provide a lifelong strategy to control the disease through maintenance therapy. After first-line chemotherapy, complete responders have reasonably long remissions in the absence of any intervening therapies, but this is not likely to be the case with recurrent disease. In fact, Markman et al[1] have stressed that remissions following treatment for recurrence are never longer than the preceding ones.

Second-Line Treatments
If maintenance has a role following first-line treatment—as argued by the results of Gynecologic Oncology Group (GOG) 178, which showed prolongation of disease-free survival with 1 year of maintenance paclitaxel[2]—should it have an even larger role in treatment planning following recurrences? While this strategy is logical, it is not proven. Still, patients who recur and then subsequently respond to treatment have beaten the odds. Such patients may be loathe to stop being treated and may request such therapy, regardless of available data. Of the second-line treatments available, pegylated doxorubicin (Doxil), with its 4- to 6-week schedule and relatively mild toxicity profile, may be the most practical for a maintenance strategy, and we have described its safety in 18 patients with gynecologic cancer maintained for 1 year or more.[3] Other drugs such as topotecan (Hycamtin) also appear to be free of cumulative toxicities, but this agent's conventional daily x 5 day schedule may be inconvenient for the patient.[4] The role of biologic agents in this setting is a matter for current and future investigation.

Bowel Complications
Bowel complications present a continuing challenge in the management of patients with ovarian cancer, and these are given comprehensive coverage by the authors. Again, the management goal in these situations is often palliation at best. It is telling that in an article promising "modern management," one of three tables details a low-residue diet. Evidence-based management of malignant bowel obstruction will not be readily determined (we recall a heated discussion at the July 2005 GOG meeting in Baltimore), as these situations require individual attention on a case-by-case basis, with decisions often factoring in intangibles, not applicable to any decision tree. Unfortunately, our success in this situation has not changed despite other advances in the field. Could there be a strategy for the prevention of such bowel complica complications? The seriousness of small bowel obstruction provides an additional rationale for maintaining the disease in remission. It also brings into focus the pattern of peritoneal spread of the majority of ovarian cancers, and the likelihood that this problem may be better controlled by intraperitoneal (IP) therapy (rather than just systemic therapy) before gross disease is present.

The recent results of the third of three phase III trials by the GOG comparing IP vs IV strategies provide convincing evidence that IP cisplatin contributes to a favorable outcome.[5] Better control of
peritoneal disease and early recurrences that lead to small bowel obstruction may be contributing to the observed survival advantage of IP therapies. As this strategy for first-line ovarian cancer treatment continues to meet resistance predominantly because of practical considerations, it is worth emphasizing that the powerful pharmacodynamic rationale for IP therapy (as borne out by the observed results) may diminish the incidence of morbid, potentially lethal bowel complications.

**Targeted Therapies**

Finally, we must direct a comment to the integration of targeted therapies with current treatments. The brief mention in the article is a reflection of the lag in testing these agents in ovarian cancer.[6] Such a lag has occurred despite a comprehensive program of drug testing from phase I to phase III by the GOG. The dominance of platinum drugs and the long array of partially effective second-line treatments account for some of this delay; however, it is time for targeted agents to be aimed directly at ovarian cancer.

For example, we are currently conducting a phase II trial investigating the small-molecule epidermal growth factor receptor (EGFR) inhibitor erlotinib (Tarceva) in combination with standard first-line therapy followed by 1 year of consolidation with the biologic agent alone in patients with ovarian, tubal, and primary peritoneal cancers. This regimen is tolerable[7] and makes scientific sense, as preclinical findings have suggested that interfering with EGFR signaling enhances the cytotoxic action of certain chemotherapeutic agents, especially the platinum compounds.

With the results of this trial and others, we will define the role of targeted agents in the management—and hopefully, the control—of ovarian cancer. Over the next few years, we expect that targeted drugs such as tyrosine kinase inhibitors and monoclonal antibodies will become fully integrated in our armamentarium. This occurrence plus the unraveling of some of the mysteries of empiric cytotoxic drug therapy, especially platinum resistance,[8] and the judicious use of surgery will continue to be the basis of the "modern" management of ovarian cancer.

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