EDITORIALS

Is It Time for Some New Approaches for Treating Advanced Ovarian Cancer?

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Advanced ovarian cancer is considered to be relatively sensitive to cytotoxic agents and is usually described in medical textbooks as a solid tumor with the potential for cure by chemotherapy. Over the past two decades, the survivorship of patients with ovarian cancer has increased, even though only fewer than 40% of all ovarian cancer patients are cured. Because attempts to develop methods for effective early diagnosis of ovarian cancer have eluded investigators, any increase in long-term survivorship must reflect either more aggressive surgical cytoreduction or more effective therapy. The development of platinum-based combination therapies in the 1980s, in conjunction with expansion of training programs in gynecologic oncology to improve primary surgery, led to data suggesting that the survival rates for ovarian cancer patients would increase *(1)*. With the introduction of the taxanes in the 1990s and their incorporation into primary chemotherapy came further improvements in survival rates *(2,3)*, although some investigators have questioned whether this class of drugs has had the impact on survival that was expected on the basis of their activities as single agents in recurrent disease *(4)*. Since the incorporation of taxanes into primary therapy for ovarian cancer, several other classic cytotoxic agents that are active in both platinum-sensitive and platinum-resistant ovarian cancers have been identified. Two of these agents, topotecan and pegylated liposomal doxorubicin, have been approved by the U.S. Food and Drug Administration for use in patients with recurrent ovarian cancer.

In this issue of the Journal, a consortium of investigators from Germany and France *(5)* report results of a trial in which patients with advanced ovarian cancer were randomly assigned to receive six to 10 cycles of carboplatin and paclitaxel—an accepted standard of care *(6)*—followed by either no additional therapy or four cycles of topotecan. The authors report that the sequential addition of topotecan did not improve the efficacy of carboplatin and paclitaxel, even among patients who had optimal surgical cytoreduction *(5)*. Also, the sequential use of topotecan was associated with more toxic effects requiring greater supportive care, although this increased toxicity was not reflected in any declines in global quality-of-life scores. Other recent trials have produced equally disappointing results. For example, the German/French consortium previously reported that adding epirubicin did not improve the efficacy of carboplatin and paclitaxel for the treatment of advanced ovarian cancer *(7)*. The Multicenter Italian Trials in Ovarian Cancer (MITO-1) study also compared topotecan as consolidation therapy after an initial response to carboplatin and paclitaxel versus no consolidation and reported no effect of consolidation on progression-free survival *(8)*. Finally, results were recently reported for a large international trial of more than 4000 patients that compared the carboplatin–paclitaxel doublet (8 cycles) with two triplet therapies and two sequential doublet therapies *(9)*. The triplet therapies consisted of carboplatin and paclitaxel with addition of either gemcitabine or pegylated liposomal doxorubicin, and the sequential doublet therapies used four cycles of either carboplatin and gemcitabine or carboplatin and topotecan, each followed by four cycles of carboplatin and paclitaxel. Once again, neither the triplet therapies nor the sequential doublet therapies improved outcomes compared with standard continuous carboplatin and paclitaxel, and toxicity was greater in some of the experimental arms *(9)*. Thus, one decade after the platinum and taxane doublet was accepted by most oncologists as the standard of care in advanced ovarian cancer, several trials that have tested the addition of agents having demonstrated activity as single agents against recurrent ovarian cancer have failed to show that these agents improve any outcome measure. Where do we go from here?

Was this failure expected? Perhaps these collective data invalidate the use of these particular drugs or the concept of using triplets or even sequential therapies to treat advanced ovarian cancer. However, neither the present study *(5)* nor the MITO-1 study *(8)* really addresses the issue of the efficacy of prolonged maintenance therapy in a well-defined population of patients who have a clinical complete response. In the present study, patients were randomly assigned before they began any treatment, so some patients were actually receiving "consolidation" for persistent disease. In the MITO-1 study, the consolidation therapy was brief (i.e., 16 weeks). By contrast, a study by Markman et al. *(10)* that provided consolidation for 1 year following primary therapy reported that prolonged maintenance therapy with paclitaxel (i.e., 12 months versus 3 months) was associated with longer progression-free survival but not with longer overall survival, and this benefit appeared to be limited to patients with the lowest CA-125 levels (and, presumably, the lowest tumor burdens) at study entry. The "benefit" was at the cost of more toxicity. Perhaps what works in one tumor (breast cancer) does not work in another.

By contrast, data from breast cancer chemotherapy trials suggest that combining three active drugs improves outcomes. Mature data evaluating the impact of taxanes in adjuvant treatment of breast cancer appear to demonstrate a beneficial effect primarily in hormone receptor–negative patients *(11,12)*. A similar discordance has been seen between breast and ovarian cancer with respect to trastuzumab. For breast cancers that overexpress the receptor tyrosine kinase HER2/neu, the monoclonal

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antibody trastuzumab has been shown to generate a response in 20% of patients with metastatic disease, improve outcomes in metastatic disease when combined with cytotoxic therapy, and statistically significantly improve all outcome measures (all $P<.001$) when used in the adjuvant setting in high-risk, HER2/neu–positive patients *(13)*. Unfortunately, trastuzumab is not a viable treatment option for ovarian cancer because the rates of HER2/neu overexpression are less than half that seen in breast cancer, and the response rates with trastuzumab in the few patients who do overexpress HER2/neu are depressingly low *(14)*.

Perhaps a more promising approach for ovarian cancer chemotherapy is to target angiogenesis, which seems to be a common theme among many types of solid tumors. Paley et al. *(15)* found that overexpression of vascular endothelial growth factor was the single most important prognostic factor for risk of recurrence in women with stage I/II ovarian cancer. The monoclonal antibody bevacizumab, which inhibits the function of vascular endothelial growth factor, has good single-agent activity against recurrent ovarian carcinomas *(16)* and has improved outcomes in colorectal *(17)*, breast *(18)*, and lung *(10)* cancers when combined with chemotherapy. A Gynecologic Oncology Group trial (ClinicalTrials.gov Identifier: NCT00262847) is now under way to compare carboplatin and paclitaxel with or without bevacizumab given either concomitantly with cytotoxic therapy or concomitantly with cytotoxic chemotherapy then followed by maintenance bevacizumab for another year in patients with advanced ovarian cancer, but accrual has been slow. The reasons given for the poor accrual to this study include patient bias—either for or against the new therapy—and the double-blind study design, which exposes some patients to placebo for months. Also, one wonders if the poor accrual might also be due to physician bias; i.e., bevacizumab is commercially available, making it possible to treat off-protocol with what might be "best therapy." But, as noted above, what works for breast cancer may not work for ovarian cancer. Other interesting targeted therapies that should be high priority for evaluation in ovarian cancer include compounds with new mechanisms of action that target tumor angiogenesis and that are or soon will be Food and Drug Administration approved for other indications, such as renal cell carcinoma or gastrointestinal stromal tumors. Some of these agents target multiple receptor tyrosine kinases (e.g., sunitinib) or more downstream pathways, such as the Raf kinase (e.g., sorafenib).

It seems that we are at a turning point in the design of clinical trials for ovarian cancer. We can continue to ask easier and, in my opinion, less important questions, such as whether cytotoxic agents should be used intravenously or intraperitoneally or whether maintenance therapy with one of the taxanes improves survival. Or we can "bite the bullet" and use all our valuable patient resources to evaluate whether ovarian cancer responds to the targeted therapies as other solid tumors have. It is no mystery why cancers of the lung, colon, and breast are often the first to be targeted by small-molecule technology: They are the most common tumors. Should not ovarian cancer follow in kind since it too is relatively common and considered relatively sensitive to therapy? Ovarian cancer seems just as likely as these other solid tumors to benefit, but only well-designed and -executed trials will tell us for sure. I ask the community of gynecologic oncology trialists to move forward and meet the challenge ahead. We owe it to our patients.

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