Editorial

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Should studies of maintenance therapy be maintained in women with ovarian cancer?

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The incidence of epithelial ovarian cancer varies throughout the world, with higher frequencies in Europe, North America, and Australia, and lower frequencies in much of Asia, Central America, South America, and North Africa. However, regardless of geography, ovarian cancer is associated with the highest case-fatality ratio among the gynecologic cancers, reflecting early peritoneal dissemination with advanced-stage disease at diagnosis. Patients undergo cytoreductive surgery and chemotherapy, generally with carboplatin and paclitaxel, and frequently achieve clinical complete remission. Modest incremental improvements in median progression-free survival (PFS) or overall survival (OS) have been achieved with the incorporation of paclitaxel, utilization of intraperitoneal therapy in selected patients, and dose-dense weekly scheduling of paclitaxel. However, these strategies have not yet been shown to have an impact on overall mortality.

Efforts to incorporate a third cytotoxic agent have not been successful, including triplet combinations, sequential doublets, alternative taxanes, and extended maintenance after completion of primary chemotherapy. In general, maintenance chemotherapy has not been associated with improved clinical outcomes in other solid tumors, and is clearly associated with an increased risk of cumulative toxicity. In women with ovarian cancer, all studies using chemotherapy have been negative [1-5], with the possible exception of one study with paclitaxel, comparing 3 vs. 12 cycles on a three-week schedule [6]. At interim analysis, an early difference in PFS favored extended therapy, and the trial was closed by recommendation of the data monitoring committee. Of note, the absolute difference in PFS (approximately 7 months) was less than the difference in treatment duration (9 months) between the two arms. These premature results remain controversial, due to the uncertain clinical benefit associated with a modest improvement of PFS without any benefit in overall survival, and at the expense of host toxicity. Gynecologic Oncology Group (GOG) is currently completing a three-arm phase III trial (GOG0212) to resolve this question, comparing observation without immediate therapy to paclitaxel for 12 months or polyglutamated paclitaxel for 12 months. Interim safety analysis has not mandated any changes in the trial design, and accrual should be completed by mid-2013. Other studies of maintenance paclitaxel have been negative [5], and there is not currently any established role for maintenance chemotherapy in women with ovarian cancer. When the Gynecologic Cancer InterGroup (GCIG) reviewed this question at a prior consensus conference, it was recommended that primary endpoints for phase III trials should be based on OS, or a substantial improvement in PFS (greater than 12 months), which would generally be associated with clinical benefit. To date, none of the maintenance trials have met these goals.

Maintenance therapy can also contribute to chemotherapy resistance, which can emerge rapidly, through multiple molecular pathways, and has been difficult to overcome. However, clinical data with inhibitors of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP), particularly in tumors with pre-existing defects in homologous recombination DNA repair are encouraging. Two randomized phase II trials with olaparib in recurrent disease have demonstrated

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a marked improvement in PFS, and the initiation of front-line phase III randomized trials that incorporate maintenance therapy are anticipated [7].

Efforts to target the epidermal growth factor receptor family, including HER2 and EGFR, with antibodies and small-molecule inhibitors of the receptor-associated tyrosine kinase (rTKI) have not been very encouraging in recurrent ovarian cancer. In addition, a phase III randomized trial evaluated the role of maintenance erlotinib, demonstrating increased toxicity without evidence of clinical benefit [8].

Tumor-associated angiogenesis has emerged as a prominent area of investigation, based on the role of vascular endothelial growth factor (VEGF) in normal ovarian physiology, as well as VEGF-mediated production of ascites, and over-expression of VEGF by the majority of high-grade tumors. Two phase III randomized trials have been completed with bevacizumab administered during and following primary chemotherapy, achieving a modest, and transient, benefit in progression-free survival, but without evidence of an advantage in overall survival for the entire enrolled population [9,10]. Again, these results raise questions about balancing potential short-term clinical benefit with treatment-related toxicities and the overall financial cost associated with long-term drug administration. Additional phase III trials are in progress, including multi-targeted rTKIs (pazopanib and nintedanib) and an antibody directed against angiopoietin-2 (AMG-386).

The current trial, as reported in this issue [11], describes the feasibility, safety, and clinical outcomes from a non-randomized phase II evaluation of maintenance docetaxel. Historically, it was suggested that docetaxel would be more effective than paclitaxel based on potency, binding kinetics, and molecular targeting. However, there are no clinical data to indicate superiority of docetaxel when compared to paclitaxel in the management of newly diagnosed or recurrent epithelial ovarian cancer. Substitution of docetaxel is a good alternative to paclitaxel in the front-line setting with a reduced risk of neuropathy and hypersensitivity reactions, but with an increased risk of dose-limiting hematologic toxicity, based on a phase III trial [12].

The current trial was carefully conducted, the results are clearly reported, and the authors appropriately conclude that 6 cycles of maintenance docetaxel can be safely administered with expected toxicity in previously-treated patients. However, no primary study hypothesis or statistical methods for key clinical outcomes were provided to justify the sample size (20 patients), and it is not possible to determine if the long-term clinical outcomes (OS and PFS) are sufficiently interesting to justify additional studies. This is a common limitation of small non-randomized studies in ovarian cancer. The data are also further limited by selection bias, as a chemotherapy maintenance trial would tend to accrue patients with more favorable prognostic factors, such as small-volume residual disease, excellent performance status, good nutritional status, and ability to tolerate additional chemotherapy.

Optimal primary therapy of advanced ovarian cancer has not substantially changed over the last few years, in spite of new cytotoxic agents, and evaluation of diverse treatment strategies. A role for maintenance therapy using conventional cytotoxic agents has not been established, and the current feasibility trial does not provide sufficient data to justify new phase III trials. Even with active targeted agents, such as bevacizumab, the analysis of risks, benefits, and financial cost are complex. Importantly, none of the reported trials have achieved benefits in OS, or prolongation of PFS greater than 12 months.

Should studies of maintenance therapy be "maintained"? Perhaps the most compelling data have emerged from randomized phase II trials of PARP inhibitors, including maintenance in the setting of recurrent disease. These trials have prompted at least two front-line phase III trials that incorporate maintenance therapy, and are anticipated to open in early 2014. Future phase III randomized trials of maintenance with conventional cytotoxic chemotherapy should not be considered without compelling data from well-designed randomized phase II trials.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Bolis G, Danese S, Tateo S, Rabaiotti E, D'Agostino G, Merisio C, et al. Epidoxorubicin versus no treatment as consolidation therapy in advanced ovarian cancer: results from a phase II study. Int J Gynecol Cancer 2006;16 Suppl 1:74-8.
2. Pfisterer J, Weber B, Reuss A, Kimmig R, du Bois A, Wagner U, et al. Randomized phase III trial of topotecan following carboplatin and paclitaxel in first-line treatment of advanced ovarian cancer: a gynecologic cancer intergroup trial of the AGO-OVAR and GINECO. J Natl Cancer Inst 2006;98:1036-45.
3. De Placido S, Scambia G, Di Vagno G, Naglieri E, Lombardi AV, Biamonte R, et al. Topotecan compared with no

 http://dx.doi.org/10.3802/jgo.2013.24.2.105

therapy after response to surgery and carboplatin/paclitaxel in patients with ovarian cancer: Multicenter Italian Trials in Ovarian Cancer (MITO-1) randomized study. J Clin Oncol 2004;22:2635-42.
4. Piccart MJ, Floquet A, Scarfone G, Willemse PH, Emerich J, Vergote I, et al. Intraperitoneal cisplatin versus no further treatment: 8-year results of EORTC 55875, a randomized phase III study in ovarian cancer patients with a pathologically complete remission after platinum-based intravenous chemotherapy. Int J Gynecol Cancer 2003;13 Suppl 2:196-203.
5. Pecorelli S, Favalli G, Gadducci A, Katsaros D, Panici PB, Carpi A, et al. Phase III trial of observation versus six courses of paclitaxel in patients with advanced epithelial ovarian cancer in complete response after six courses of paclitaxel/platinum-based chemotherapy: final results of the After-6 protocol 1. J Clin Oncol 2009;27:4642-8.
6. Markman M, Liu PY, Wilczynski S, Monk B, Copeland LJ, Alvarez RD, et al. Phase III randomized trial of 12 versus 3 months of maintenance paclitaxel in patients with advanced ovarian cancer after complete response to platinum and paclitaxel-based chemotherapy: a Southwest Oncology Group and Gynecologic Oncology Group trial. J Clin Oncol 2003;21:2460-5.
7. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med 2012;366:1382-92.
8. Vergote IB, Joly F, Katsaros D, Coens C, Reinthaller A, Hall M, et al. Randomized phase III study of erlotinib versus observation in patients with no evidence of disease progression after first-line platin-based chemotherapy for ovarian carcinoma: a GCIG and EORTC-GCG study [abstract]. J Clin Oncol 2012:30(18 suppl);LBA5000.
9. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 2011;365:2473-83.
10. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 2011;365:2484-96.
11. Isonishi S, Suzuki M, Nagano H, Takagi K, Shimauchi M, Kawabata M, et al. A feasibility study on maintenance docetaxel after paclitaxel-carboplatin chemotherapy in patients with advanced ovarian cancer. J Gynecol Oncol 2013;24:154-9.
12. Vasey PA, Jayson GC, Gordon A, Gabra H, Coleman R, Atkinson R, et al. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. J Natl Cancer Inst 2004;96:1682-91.