New developments in the anti-neoplastic drug management of ovarian cancer
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Abstract

Over the past several years, there have been a number of relevant evidence-based randomized trials that have the potential to change the standard management paradigm in the malignancy of ovarian cancer and (most importantly) enhance clinically relevant outcomes. This commentary will briefly review these trials.

Bevacizumab in the treatment of ovarian cancer

Four randomized trials have been reported in three specific clinical settings that clearly document both the biological and clinical impact of bevacizumab, a human recombinant monoclonal antibody directed against vascular endothelial growth factor (Table 1) [1-4]. However, while there has been a documented improvement in progression-free survival (PFS) in each of the studies, they have failed to reveal superior overall survival for patients managed on the bevacizumab-containing treatment arm.

While it is recognized that not all agree on the interpretation of these findings, it is the opinion of this commentator that it is highly likely the failure to convert a statistically significant improvement in PFS to superior overall survival is a direct result of the fact that the large majority of ovarian cancer patients receive multiple anti-neoplastic agents (including possibly bevacizumab) previously demonstrated to have both biological and clinical activity in ovarian cancer after they complete treatment on the study, which may favorably impact their ultimate survival [5].

Despite the solid evidence-based results of these multiple phase 3 randomized trials (and perhaps at least partly because of them), there remain many quite relevant unanswered questions regarding the optimal utilization of bevacizumab in the management of ovarian cancer (Table 2). Hopefully, future clinical trials will help resolve the uncertainties surrounding the use of this important anti-neoplastic agent. The urgency in providing these answers is heightened when one recognizes the major financial impact associated with the routine administration of bevacizumab.

Other anti-angiogenic agents in ovarian cancer

A preliminary report of the results of a phase 3 trial examining a potential role for pazopanib employed as a “maintenance” strategy following the completion of primary cytotoxic chemotherapy has revealed that the administration of this agent (compared to placebo) improves PFS (median 17.9 months versus 12.3 months; \( P = 0.0021; \) hazard ratio [HR] 0.766) [6]. Although data on overall survival remain immature, the initial reported data do not suggest this strategy improves overall survival. Similar to the previously discussed situation with bevacizumab, this outcome is highly likely to be a result of the multiple anti-neoplastic agents delivered to patients once they have completed treatment on this trial [5]. Data from phase 3 trials examining several additional anti-angiogenic drugs (nintedanib; cediranib; trebananib) in ovarian cancer management are eagerly awaited [7].

Olaparib in the management of ovarian cancer

Phase 2 trials have previously demonstrated the clinical activity of single-agent olaparib, a poly(ADP-ribose)
polymerase (PARP) inhibitor, in ovarian cancer patients with a germline BRCA 1 or BRCA 2 mutation [8]. As preclinical data revealed similarities in the molecular profiles of BRCA mutation-positive ovarian cancers and non-mutant-positive high-grade serous ovarian tumors, investigators conducted a phase 2 randomized trial (n = 265 patients) comparing olaparib to “placebo” employed as a single-agent “maintenance” strategy in women with high-grade serious ovarian cancers who had achieved a response or exhibited stable disease following a second-line platinum-based chemotherapy regimen [9]. The study revealed a highly statistically significant improvement in PFS (median 8.4 months versus 4.8 months; \( P < 0.001; \) HR 0.35) in favor of the olaparib strategy. Again, there was no difference in overall survival between the study groups [5].

In a preliminary report of a re-evaluation of this study population, the investigators were able to examine 218 (of the original 265) patients for the presence of germline BRCA mutations [10]. This analysis revealed an even greater impact of olaparib (compared to placebo) on PFS (median 11.2 months versus 4.1 months; \( P < 0.001; \) HR 0.17) in patients with a germline BRCA mutation. It was also noted that of the 37 patients with a known germline BRCA mutation who were treated with “placebo” in this trial, 13 subsequently received a PARP inhibitor (in addition to other biologically active agents this group of patients may have also received following completion of the trial), potentially seriously compromising an analysis of an overall survival endpoint in this study [5].

**Cytotoxic anti-neoplastic agents**

Despite the enthusiasm for the development of novel anti-neoplastic agents in ovarian cancer, it must be remembered that classical “cytotoxic” anti-neoplastic agents (e.g. the “platinums”, the “taxanes”) remain the cornerstone in disease management. Furthermore, clinical research designed to optimize the utilization of such
agents remains active in the gynecologic oncology investigative community.

For example, a phase 3 randomized trial revealed the superiority (PFS endpoint) of paclitaxel plus pegylated liposomal doxorubicin compared to carboplatin plus paclitaxel in recurrent, potentially platinum-sensitive, ovarian cancer [11], possibly due to a provocative, essentially unexplained, and striking reduction in carboplatin-associated hypersensitivity reactions when this agent is delivered with pegylated liposomal doxorubicin in the second-line setting [11,12].

There has been a particular focus on strategies designed to optimize the method of paclitaxel administration in ovarian cancer. The Japanese Gynecologic Oncology Group reported the results of a phase 3 trial demonstrating the superiority (PFS and overall survival) associated with administering paclitaxel on a weekly (80 mg/m² per week) schedule compared to the “standard” every-3-week regimen [13]. In this program, the carboplatin was delivered every 3 weeks.

In a preliminary report of a multi-institutional phase 3 randomized trial, investigators explored a quite different “weekly strategy” with both the paclitaxel (60 mg/m² per week) and carboplatin (AUC 2/week) administered by this novel approach [14]. Compared to “standard” every-3-week carboplatin plus paclitaxel, the weekly (paclitaxel and carboplatin) schedule was revealed to produce equivalent efficacy but with substantially reduced side effects. Whether the differences in efficacy and toxicity outcomes between these two studies relate to the weekly dose of paclitaxel delivered, the approaches to the administration of carboplatin, unique genetic or environmental backgrounds of the patient populations, or a combination of these factors remains unknown and worthy of future investigative efforts.

**Abbreviations**

HR, hazard ratio; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival.

**Disclosures**

I would list potential “conflicts of interest” to include participation in medical advisory boards for: Genentech, Glaxo-Smith Kline, Amgen, Boehringer-Ingelheim, Celgene, Novartis.

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