The use of bevacizumab in the management of ovarian cancer: an argument for single-agent rather than combination therapy

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Bevacizumab is a biologically and clinically active antineoplastic agent in the management of epithelial ovarian cancer. While phase III trial data have revealed the favorable impact on progression-free survival associated with combining the agent with cytotoxic chemotherapy, at the current time a strong argument can be made (based on both efficacy and cost-effectiveness considerations) that a more rational approach to utilizing bevacizumab in ovarian cancer would be to administer the drug as a single agent in the platinum-resistant setting.

Key words: ovarian cancer, bevacizumab, efficacy, toxicity, cost-effectiveness

introduction

There is a critical need to develop new agents in epithelial ovarian cancer that are both biologically and (most relevant) clinically active in patients whose disease has been shown to be resistant to platinum-based therapy, either delivered in the primary setting or following progression of a second-line platinum-based approach [1]. In addition, due to the inherent acute, chronic and cumulative toxicities of existing routinely employed cytotoxic antineoplastic therapy (e.g. bone marrow suppression, emesis, neuropathy, renal dysfunction etc.), it will be important to develop novel agents that demonstrate side-effect profiles very different from these established classes of drugs.

The physiologic and pathologic process of ‘angiogenesis’ has been shown in both pre-clinical model systems and in retrospective clinical evaluation to be relevant in both the biological progression of ovarian cancer and in predicting a more unfavorable outcome [2–4]. As a result, it is not surprising that there has been considerable interest within the gynecologic cancer research community to explore the potential clinical utility of antiangiogenic agents as a strategy to successfully manage this malignancy.

bevacizumab in ovarian cancer

Bevacizumab, a monoclonal antibody that targets the vascular endothelial growth factor, has been shown in several well-designed and conducted phase II clinical trials to possess a highly relevant degree of biological and clinical activity when administered as a ‘single agent’ in both recurrent and well-defined platinum-resistant ovarian cancer (15%–20% objective response rate) [5, 6]. In one trial there was evidence of a population-based prolonged time to disease progression following delivery of the agent compared with a reasonably matched historical control patient group given a variety of cytotoxic drugs and treated by the same group of clinical investigators [3].

These studies have revealed that the toxicity profile of single-agent bevacizumab in this specific clinical setting is comparable to that observed when the drug is administered to other malignancies, with hypertension being the major acute side-effect requiring management [5, 6]. However, in several reports, a rather higher incidence of bowel perforation (up to a 10% risk) was observed in women with ovarian cancer versus prior reports of this serious toxicity in the oncology literature in other patient populations [6, 7]. Of interest and clinical relevance, limited but intriguing data suggest the presence of air fluid levels or a thickened bowel wall observed on radiographic imaging may be helpful in identifying ovarian cancer patients who are at particular risk for this concerning toxicity of therapy and should probably not receive the agent [6].

A number of reports have described nonrandomized experiences with combining bevacizumab and cytotoxic chemotherapy, and have suggested a higher objective response rate compared with the administration of the antiangiogenic agent alone [8–11]. However, there are currently ‘no randomized (either phase II or III) data’ available to suggest this outcome is anything more than selection bias or that a ‘higher response rate’ (compared with the delivery of single-agent bevacizumab) will be translated into a superior ‘clinically relevant outcome’ (e.g. improved quality of life, superior symptom control, or longer progression-free or overall survival).

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phase III trials of combination cytotoxic chemotherapy with or without bevacizumab in ovarian cancer

Over the past year the preliminary results of several phase III trials that combined bevacizumab with cytotoxic chemotherapy, either as primary treatment or delivered in the second-line setting, have been reported [12–14]. Of great relevance to the current discussion, it should be noted that the control arms of these studies have been chemotherapy without the antiangiogenic drug (and not bevacizumab alone).

The trials have revealed the statistically significant favorable impact of combined treatment (platinum-based chemotherapy plus bevacizumab) on progression-free survival. However, to date, no statistically significant impact on overall survival has been documented.

critique of evidence supporting the routine use of bevacizumab in combination with cytotoxic chemotherapy in the management of ovarian cancer

It is critical to again note that despite the data demonstrating improved time-to-disease progression associated with adding bevacizumab to combination platinum-based chemotherapy (in both the primary and recurrent disease settings), there remain no data from randomized trials to document the overall superiority of such a management strategy compared with an alternative approach where single-agent bevacizumab will be administered (if clinically indicated) at some point following documentation of disease progression after one or more cytotoxic chemotherapeutic regimens.

Considering the relative safety of bevacizumab observed when the agent is delivered with platinum-based or other cytotoxic chemotherapy programs, why does it matter if the two classes of agents are given together versus the alternative approach of the antiangiogenic drug being given only after disease progression? Surely, based on the available evidence there is no reason to believe that the ‘sequential’ approach will be therapeutically superior to a combination strategy.

The answer to this question is simple: bevacizumab is very expensive [15–17]. In addition, the agent is certainly not ‘nontoxic’ [12–14, 18, 19] and retrospective (nonrandomized) data suggest an overall less favorable side-effect profile for chemotherapy plus bevacizumab versus the antiangiogenic administered alone [8].

Lastly, based on the available clinical data and the known direct cost of bevacizumab, strategies that combine this drug with chemotherapy as a component of primary treatment of ovarian cancer have ‘failed the test of being cost-effective’ in a formal analysis of this particular issue [16, 17].

This is a particularly relevant point, since there remains no reliable clinical or molecular biomarker that is capable of prospectively defining the specific patient population who may benefit from this drug. As a result, the existing first-line chemotherapy trial data would suggest ‘all patients’ who respond to the platinum-based chemotherapy program and even those whose disease has simply not progressed (so-called ‘stable disease’) will potentially require prolonged periods of therapy (including the delivery of single-agent ‘maintenance’ treatment for ≥12 months) [12, 13].

an alternative proposal for the use of bevacizumab in the management of ovarian cancer

Based on both clinical factors and cost considerations, it is rational to propose an alternative strategy for the use of bevacizumab in ovarian cancer (Table 1).

In this important discussion it is highly relevant to formally acknowledge that one quite rational interpretation of the reported front-line three-arm phase III randomized trial that compared chemotherapy alone, versus chemotherapy plus bevacizumab delivered only during the cytotoxic therapy, versus chemotherapy plus bevacizumab administered both during and following the completion of the cytotoxic drugs, is that the study ‘demonstrates the absence of either synergy or even an additive effect of the two classes of drugs’ [12]. Rather, ‘the measurable (and statistically significant) benefits of bevacizumab on progression-free survival appear to have been due solely to its administration as a single agent in the “maintenance” phase of the treatment regimen’.

If this interpretation of the existing data is correct, it is reasonable to further speculate that a similar outcome following the administration of bevacizumab would occur if the agent was delivered alone at alternative time points in the natural history of an individual ovarian cancer patient’s illness (e.g. second-, third- or fourth-line treatment of platinum-resistant disease). That is, the sequential delivery of such treatment in an individual patient whose cancer is biologically and clinically responsive to the antiangiogenic drug will be as effective as the combined use of the drug with cytotoxic chemotherapy.

Therefore, when the use of bevacizumab is clinically indicated, why not simply administer the drug as a single agent?

Table 1. Rationale for employing single-agent bevacizumab in ovarian cancer

| 1. Equivalent single-agent biological/clinical activity (nonrandomized experience) compared with any other antineoplastic agent in platinum-resistant ovarian cancer |
| 2. (Current) Absence of any randomized trial data demonstrating the superiority of the combination of chemotherapy plus bevacizumab compared with bevacizumab alone (sequential administration of ‘second-line’ cytotoxic chemotherapy followed by bevacizumab, or bevacizumab followed by ‘second-line’ chemotherapy) |
| 3. Administration of single-agent bevacizumab in a patient with measurable, evaluable (CA125) or symptomatic (e.g. large-volume malignant ascites) disease would permit an assessment of the clinical utility of the strategy following several treatment cycles. As a result, the antiangiogenic agent would ‘not be continued for prolonged periods in nonprogressing patients in the absence of clinical/biological evidence the natural history of the individual cancer has been favorably impacted by the drug’ |
Finally, and of considerable relevance in the current worldwide intensive exploration of strategies to contain the staggering rise in the costs of cancer treatment [15], one can reasonably argue that the party responsible for assuming the financial burden of bevacizumab therapy (e.g. national health system, insurance carrier or patient’s family) may be far more willing to accept this request if the justification is based on ‘unequivocal documentation’ that this treatment has resulted in ‘patient-specific objectively measurable clinical benefit’.

disclosures

Dr Markman has served as a consultant to Genentech.

references