Combination Cytotoxic and Antiangiogenic Therapy in the Management of Epithelial Ovarian Cancer

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ABSTRACT

The majority of patients with advanced epithelial ovarian cancer respond to primary platinum/taxane-based combination chemotherapy. Unfortunately, recurrence is the rule rather than the exception in this clinical setting. In addition, multiple trials focused on the addition of a “third” cytotoxic drug to a platinum/taxane combination have failed to demonstrate any improvement in outcome. However, recent data reveal that addition of the antiangiogenic agent, bevacizumab, to either a primary platinum-based chemotherapy program or platinum-based therapy to manage recurrent disease can substantially improve time to subsequent disease progression and potentially favorably

affect overall survival. This review discusses the rationale supporting the combination of cytotoxic and antiangiogenic therapy in advanced epithelial ovarian cancer, the existing evidence-based data supporting this strategy, and possible future research directions in this difficult malignancy.

Keywords: antiangiogenic therapy; combination chemotherapy; epithelial ovarian cancer

INTRODUCTION

Epithelial ovarian cancer is one of the most chemosensitive of all solid (nonhematologic) malignancies. Following primary platinum-based (most frequently, carboplatin) therapy, 60%-80% of patients will be anticipated to achieve both a major objective (eg, substantial shrinkage of measurable tumor masses, decline in serum cancer antigen 125 antigen levels) and subjective (eg, decrease in pain, reduction in malignant ascites formation) improvement in their disease (Table 1) [1]. Furthermore, a relatively large number of cytotoxic drugs have been shown to be biologically active when administered to patients whose cancers have either failed to respond to, or have progressed

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Table 1. Standard primary cytotoxic chemotherapy regimens in the management of epithelial ovarian cancer.

Carboplatin (AUC 5-7.5) plus paclitaxel (175 mg/m ² over 3 hours)
Carboplatin (AUC 6) plus paclitaxel (80 mg/m ² /week)
Carboplatin (AUC 5-6) plus docetaxel (60-75 mg/m ²)
Cisplatin (75 mg/m ²) plus paclitaxel (135 mg/m ² over 24 hours)

AUC=area under curve.

relatively quickly following the completion of platinum-based treatment [1].

Both currently employed primary and second-line chemotherapy approaches have clearly been documented to improve survival (both overall and the time to disease progression) and to have a favorable affect on cancer-associated symptoms. However, it has been recognized by the ovarian cancer research community and physicians who regularly or infrequently manage this disease that a “plateau” appears to have been reached in improving clinical outcomes by simply finding new cytotoxic drugs or by combining existing agents in novel programs [1].

For example, in an important study involving major international collaborations, 2000 patients with advanced ovarian cancer were randomized to one of four unique three-drug combination cytotoxic chemotherapy regimens or to the “gold standard” of carboplatin plus paclitaxel [2]. Unfortunately, this study revealed no difference in either progression-free survival (PFS) or overall survival between any of the treatment regimens. As a result of this and similar efforts that have failed to demonstrate improved survival outcomes associated with combining cytotoxics in this clinical setting, there has been considerable interest in discovering and subsequently testing alternative systemic treatment approaches in the management of ovarian cancer.

ANGIOGENESIS AND THE USE OF ANTIANGIOGENIC AGENTS IN OVARIAN CANCER

The process of angiogenesis has been well recognized to play a central role in normal ovarian function and reproductive physiology [3]. In addition, solid preclinical and clinical data have demonstrated the substantial negative association between evidence of a potent angiogenic effect in individual tumors (eg, high tissue expression, elevated serum levels of angiogenic factors) and overall survival in patients with ovarian cancer [4,5].

These provocative observations led investigators to explore the potential clinical utility of a number of pharmaceutical agents whose biological activity has been hypothesized to be due (at least in part) to their ability to strongly inhibit angiogenesis (antiangiogenic effect).

Bevacizumab, an inhibitor of vascular endothelial growth factor is the drug in this category that has been most extensively evaluated in the management of epithelial ovarian cancer.

Several single agent bevacizumab trials conducted in patients with ovarian cancer whose malignancy had progressed after one or more previous cytotoxic antineoplastic regimens have confirmed impressive biological activity for the drug, with approximately 15%-20% of individuals observed to have achieved a measurable effect (confirmed by response evaluation criteria in solid tumors [RECIST] criteria) [6,7]. In addition, in one cooperative group study a number of patients treated with single agent bevacizumab appeared to experience a rather unexpected extension of the time to subsequent disease progression when compared with a “historical control”

(nonrandomized) population from the same group of investigators [6].

With one important exception, the toxicity profile identified in these studies was similar to that observed in other settings where single agent bevacizumab had been evaluated in the past. An unexpected relatively high incidence of bowel perforations (approximately 10%) was noted in one phase 2 trial, with similar experiences noted by other investigators [7]. Of interest and potentially of considerable clinical relevance despite limited data, there appeared to be an association identified in this trial between the extent of bowel involvement with tumor (based on either radiographic evidence of “thickened bowel wall” or partial small bowel obstruction) and the subsequent risk of development of bowel perforation.

A number of investigators have also reported nonrandomized phase 2 studies, or retrospective reviews of individual institutional experiences, combining bevacizumab with cytotoxic agents in the treatment of ovarian cancer [8,9]. However, based on these uncontrolled reports it remained unknown if any hypothesized improvement in outcome (eg, response, extended period of time to disease progression) was superior to alternative strategies, including the sequential administration of cytotoxic therapy followed by the antiangiogenic agent, or the reverse sequence.

PHASE 3 TRIALS OF COMBINATION CYTOTOXIC CHEMOTHERAPY WITH OR WITHOUT BEVACIZUMAB IN THE PRIMARY MANAGEMENT OF EPITHELIAL OVARIAN CANCER

At the time of writing this review, the preliminary results of three phase 3 randomized trials, which examined a potential role for bevacizumab when combined with standard

cytotoxic chemotherapy in the management of ovarian cancer, have been reported [10–12]. Two of these studies evaluated the addition of the antiangiogenic agent with carboplatin plus paclitaxel in the primary care setting (Table 2) [10,11], while the third trial explored the drug in recurrent disease when given with carboplatin plus gemcitabine (Table 3) [12].

In the first primary chemotherapy treatment trial to be reported, investigators from the Gynecologic Oncology Group (GOG) randomized patients with stage III and IV ovarian cancer to one of three study arms (Table 2) [10]. Of considerable interest, this study was unique in the spectrum of all oncology trials exploring a role for antiangiogenic drugs in that it specifically addressed two different but highly clinically relevant issues associated with the use of bevacizumab.

The first question was whether the antiangiogenic agent’s activity was based exclusively on its ability to potentiate the favorable effects of the simultaneously administered chemotherapy. This might happen because of the drug’s ability to enhance the delivery of cytotoxic therapy to the tumor due to improved blood supply.

The second question was whether the antiangiogenic agent would have a favorable impact on outcome, potentially entirely independent of the chemotherapy, when administered as a “maintenance” approach after completing delivery of the cytotoxics. A proposed mechanism for such an effect would be interference by bevacizumab with the cancer’s ability to develop new blood vessels to permit local tumor growth or more distant metastatic spread.

As outlined in Table 2 [10,11], patients treated with bevacizumab both during chemotherapy and after completion of cytotoxic therapy (“maintenance”) experienced a statistically

Table 2. Phase 3 trials comparing carboplatin plus paclitaxel with or without bevacizumab as primary chemotherapy of epithelial ovarian cancer.

Regimen	PFS (median)	Preliminary overall survival (median)
GOG trial [10]		
Carboplatin/paclitaxel	10.3 months	39.3 months
Carboplatin/paclitaxel + bevacizumab (delivered only during chemotherapy)	11.2 months (hazard ratio: 0.908; $P=0.80$)	38.7 months
Carboplatin/paclitaxel + bevacizumab (delivered with chemotherapy and as single agent “maintenance”)	14.1 months (hazard ratio: 0.717; $P<0.001$)	39.7 months
ICON 7 [11]		
Carboplatin/paclitaxel	17.4 months	Not available
Carboplatin/paclitaxel + bevacizumab (delivered with chemotherapy and as single agent “maintenance”)	19.8 months (hazard ratio: 0.87; $P=0.039$)	Not available

GOG=Gynecologic Oncology Group, PFS=progression-free survival.

significant improvement in PFS compared with chemotherapy alone (no bevacizumab). At the time of the initial study, follow-up was not sufficient to make a definitive comment regarding overall survival (preliminary data shown in Table 2), although there was no difference in 1-year survival between this study arm and the chemotherapy only “control group.”

Of considerable interest, and to the surprise of many, there was no difference in PFS between patients who received the antiangiogenic agent solely during chemotherapy (no “maintenance” bevacizumab), compared with carboplatin plus paclitaxel alone (Table 2). One-year survival was also not different from the “control group.”

The second primary ovarian cancer phase 3 bevacizumab trial, which was conducted in Europe and Canada, differed in several important aspects compared with the GOG study (Table 2) [11]. First, this study did not employ placebo control. Second, the dose of bevacizumab was one-half (7.5 mg/kg every 2 weeks) the dose utilized in the GOG trial

(15 mg/kg). Third, patients with somewhat earlier stage disease were permitted entry into the European/Canadian study. Finally, this trial had only two arms, a “control regimen” of carboplatin plus paclitaxel and an experimental program that included bevacizumab delivered both during chemotherapy and as single agent “maintenance” when cytotoxics were discontinued.

Again, this study, which to date has only been presented in abstract form, revealed a statistically significant improvement in PFS in favor of the experimental program, with no statistically significant impact on overall survival [11]. In an interesting subset analysis, patients with the most extensive disease (stage IIIC and IV) appeared to experience the greatest benefit from the addition of bevacizumab to carboplatin and paclitaxel.

Additional follow-up data from both primary chemotherapy studies, particularly any influence of therapy on overall survival, are awaited with considerable interest.

PHASE 3 TRIAL OF CYTOTOXIC CHEMOTHERAPY WITH OR WITHOUT BEVACIZUMAB IN RECURRENT OVARIAN CANCER

A preliminary report of the results of adding bevacizumab to carboplatin plus gemcitabine in recurrent ovarian cancer appears to have reached similar conclusions to that of the previously described primary phase 3 studies demonstrating a statistically significant improvement in PFS associated with combining the antiangiogenic agent with chemotherapy (Table 3) [12]. Further, this strategy was associated with an increase in the objective response rate, compared with carboplatin plus gemcitabine alone.

Of note, while chemotherapy was administered for a fixed number of cycles the antiangiogenic agent was actually continued (assuming acceptable toxicity) until documented disease progression rather than being stopped at some rather arbitrary time point (eg, six cycles of therapy, two cycles beyond “stabilization of the disease process”).

While it remains to be determined if the demonstrated favorable impact of treatment on PFS observed in this trial will be translated into a statistically significant difference in overall survival, the preliminary study results suggest this is a possible outcome. Therefore, it is reasonable to inquire why these results may differ from what has been observed to date in primary disease management studies.

First, as previously noted and in sharp contrast to front-line trials where treatment was discontinued after 12 (European/Canadian study) or 15 months (GOG study), bevacizumab was continued until documented disease progression in the recurrent disease study [12]. Second, with the more modest impact of platinum-based chemotherapy on outcome in recurrent disease (compared with primary therapy), realistically, a possible favorable influence of the antiangiogenic drug on the course of illness in this specific setting may have been easier to observe.

Again, as with the primary disease management studies, the final results of this effort are awaited with considerable interest. A confirmatory phase 3 trial examining the combination of chemotherapy with or without bevacizumab in recurrent ovarian cancer is being conducted by GOG and remains in progress. It is anticipated the preliminary results of this trial will be available within the next 1 to 2 years.

OTHER ANTIANGIOGENIC AGENTS BEING STUDIED IN COMBINATION WITH CHEMOTHERAPY IN EPITHELIAL OVARIAN CANCER

Several phase 2 and phase 3 comparative trials have been initiated that explore the clinical utility of a number of additional antiangiogenic agents (cediranib, pazopanib, BIBF 1120, vascular endothelial growth factor-trap,

Table 3. Phase 3 trial comparing carboplatin plus gemcitabine with or without bevacizumab in (potentially) platinum-sensitive recurrent ovarian cancer [12].

Regimen	Response rate	PFS (median)	Overall survival
Carboplatin + gemcitabine	57.4%	8.4 months	29.9 months
Carboplatin + gemcitabine + bevacizumab	78.5% ($P<0.0001$)	12.4 months (hazard ratio: 0.484; $P<0.0001$)	35.5 months (hazard ratio: 0.751; $P=0.094$)

PFS=progression-free survival.

sorafenib, sunitinib, and AMG 386) when combined with cytotoxic chemotherapy in managing epithelial ovarian cancer [13].

It is still not known if any agent will be seen as superior to bevacizumab in this setting, in either terms of improved survival or reduced toxicity. It is certainly possible that a future study will directly compare the utility of two or more antiangiogenic approaches. It is also reasonable to consider combining two antiangiogenic agents with different mechanisms of biological activity as treatment for ovarian cancer. However, the potential for enhanced toxicity would be realistically a concern in this setting [14].

CONCLUSION

Remaining preliminary, existing data support a potentially highly relevant role for combining cytotoxic chemotherapy with bevacizumab (or possibly other antiangiogenic agents) in the management of advanced epithelial ovarian cancer. However, it is relevant to acknowledge that at the present time it remains unknown if the planned sequential delivery of chemotherapy and antiangiogenic therapy (eg, primary chemotherapy with bevacizumab followed by single agent maintenance bevacizumab) might produce equivalent outcomes and possibly a meaningful reduction in the risk of serious side effects. Future research in this area appears warranted.

While not the focus of this review, one final comment is necessary in this discussion of a role for antiangiogenic agents in the noninvestigative management of ovarian cancer. It is recognized that the substantial costs associated with many novel antineoplastic agents, including antiangiogenic drugs, may limit their use despite demonstrated improvement in clinically meaningful

endpoints (eg, time to symptomatic disease progression).

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