integrating bevacizumab into the management of epithelial ovarian cancer: the controversy of front-line versus recurrent disease

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angiogenesis plays a fundamental role in the pathogenesis of ovarian cancer. vascular endothelial growth factor (vegf) expression has been associated with the development of malignant ascites and tumor progression. bevacizumab (avastin®, genentech, south san francisco, ca, usa), a humanized anti-vegf monoclonal antibody, is the most widely studied antiangiogenesis agent across tumor types and specifically in epithelial ovarian cancer (eoc). with the recent reporting of four consecutive positive randomized trials adding bevacizumab to chemotherapy in the treatment of both front-line (gog 218 and icon7) and recurrent eoc (‘platinum-resistant’ aurelia trial) or ‘platinum-sensitive’ (oceans trial), the most debatable question today is thus not if we should treat ovarian cancer patients with bevacizumab, but when. as bevacizumab is active in both settings, it seems appropriate to carefully consider this clinical controversy: ‘what is the optimal setting for bevacizumab treatment?’ a fine balance of efficacy, toxicity, quality of life, and symptom control is the main crux of this controversy. the cost effectiveness of bevacizumab in eoc is also controversial

key words: ovarian cancer, front-line, recurrent disease, bevacizumab, antiangiogenesis, controversies

introduction

in the 1990s, platinum/taxane combination chemotherapy supplanted cisplatin/cyclophosphamide and became the international standard of care for the first-line treatment of advanced ovarian cancer, including fallopian tube and primary peritoneal carcinomas collectively known as epithelial ovarian cancer (eoc). despite initial chemo-sensitivity to platinum/taxane doublets, most patients with advanced eoc relapse after first-line therapy. thus, more effective front-line therapies are needed to improve response rates and prolong progression-free survival (pfs), thereby improving both the quality and length of life following the diagnosis of advanced eoc. additionally, since effective salvage treatments are lacking, better approaches to recurrent eoc are being actively studied [1].

angiogenesis plays a fundamental role in the pathogenesis of eoc, promoting tumor growth and metastatic spread. vascular endothelial growth factor (vegf) expression has been associated with the development of malignant ascites and tumor progression [2]. bevacizumab (avastin®; genentech, south san francisco, ca, usa), a humanized anti-vegf monoclonal antibody, is the most widely studied antiangiogenesis agent across tumor types and specifically in eoc. preclinical data suggest that prolonged administration of bevacizumab as maintenance therapy after cisplatin-based chemotherapy prolongs survival by inhibiting or delaying disease recurrence in a murine ovarian cancer model [3].

in march 2005, single-agent bevacizumab at 15 mg/kg (iv) every 3 weeks was first reported to be active in a case of recurrent high-grade serous ovarian cancer after failing 11th line cytotoxic chemotherapy and radiation. an objective durable response lasting at least 5 months was documented [4]. since then, many case series [5] and phase ii trials have confirmed these results. gynecologic oncology group (gog) protocol 170-d prospectively studied single-agent bevacizumab at this dose and schedule among 62 women with recurrent ovarian cancer. thirteen (21.0%) patients had documented responses (2 complete, 11 partial; median response duration, 10 months), and 25 (40.3%) survived progression free for at least 6 months. median pfs and overall survival (os) were 4.7 and 17 months, respectively. prior platinum sensitivity, age, number of prior chemotherapeutic regimens, and performance status were not predictive of clinical activity [6].

with the recent reporting of four consecutive randomized trials adding bevacizumab to chemotherapy (summarized below) in the treatment of both front-line (gog 218 [7] and icon7 [8]) and recurrent eoc (‘platinum-resistant’ aurelia trial [9]) or ‘platinum-sensitive’ (oceans trial [10]), the most debatable question today is thus not if we should treat ovarian cancer patients with bevacizumab, but when. as bevacizumab is active in both settings, it seems...
appropriate to carefully consider this clinical controversy: ‘what is the optimal setting for bevacizumab treatment?’ In considering this question, the following issue is also relevant: ‘what are the treatment objectives in front-line and in relapsed EOC?’ The choice of the optimal setting of a new treatment in EOC is highly dependent on what can be achieved by a specific novel treatment and how it fulfills the main treatment goals expected by caregivers and patients at the different time points during the course of the disease.

In first-line treatment, tolerance to therapy is an important consideration, but the main treatment objective is to ‘cure patients’. Many simplify this goal as trying to improve OS. In the relapsed setting, however, where cure is rarely achievable, the main treatment objectives are disease and symptom control [11]. This fine balance of efficacy, toxicity, and symptom control is the main crux of this controversy.

### Efficacy of bevacizumab in ovarian cancer

Is the magnitude of disease control (PFS and OS) longer if bevacizumab is used in patients in first line rather than in relapse?

Most recently, four randomized phase III trials have been carried out adding bevacizumab to either front-line chemotherapy (GOG 218 [7] or ICON7 [8]) or to chemotherapy in ‘platinum-resistant’ (AURELIA Trial [9]) or ‘platinum-sensitive’ (OCEANS Trial [10]) recurrent EOC. Although all four studies met their primary end points of prolonging PFS (Table 1), only two suggested an improvement in OS among unique subsets of patients. In ICON7, among patients at high risk for progression, the benefit of adding bevacizumab was greatest. The estimated median PFS was 10.5 months with standard therapy, compared with 15.9 months with bevacizumab [hazard ratio (HR) for progression or death in the bevacizumab group, 0.68; 95% confidence interval (CI) 0.55–0.85; P < 0.001]. Similarly, there were 188 deaths in this group of women with FIGO stage IV disease or FIGO stage III disease and >1.0 cm of residual disease after debulking surgery (109 in the standard-therapy group and 79 in the bevacizumab group), and the median OS was increased from 28.8 months in the standard-therapy group to 36.6 months in the bevacizumab group (HR for death in the bevacizumab group, 0.64; 95% CI 0.48–0.85; P = 0.002) [8]. In GOG 218, the median OS for FIGO stage IV subjects was also increased from 32.8 months in arm 1 (placebo-containing arm) to 40.6 months in arm 3 with the addition of bevacizumab to chemotherapy plus maintenance (HR 0.72; 95% CI 0.53–0.97) [12]. Since an OS advantage is suggested in these two unique front-line settings and not in treating recurrent disease (reviewed below), one could argue that front-line therapy is the ideal place to add bevacizumab to chemotherapy. However, OS data in ICON7 remain immature with only 40% of the events having occurred in the high-risk group. In addition, the GOG 218 OS stage IV data were a post hoc subgroup analysis, whereas AURELIA OS results are still pending.

Relative to PFS, the absolute median PFS advantage of bevacizumab added to chemotherapy followed by maintenance compared with chemotherapy alone (plus placebo in GOG 218) in first-line was 3.8 months (GOG 218, from 10.3 to 14.1 months with and without bevacizumab), and 1.5 months (ICON7, from 20.3 to 21.8 months). One must note that PFS was measured in GOG 218 both by CA125 elevations and by radiologic progression (Response Evaluation Criteria In Solid Tumors [RECIST]). This is the only phase III trial where CA125 elevations were considered in the determination of progression. When CA125 elevations were censored, the PFS difference increases to a median of 6.0 months. The smaller magnitude of PFS difference in ICON7 compared with GOG 218 could be secondary to the lower dose of bevacizumab as well as a better prognosis group of patients in ICON7. The median PFS benefit as measured in months associated with adding bevacizumab to chemotherapy seems to be similar in recurrent ovarian cancer, being 4 months in platinum-sensitive relapse (OCEANS, from 8.4 to 12.4 months) and 3.3 months in platinum-resistant

<table>
<thead>
<tr>
<th>Study</th>
<th>Arms</th>
<th>Sample size</th>
<th>Median PFS (months)</th>
<th>Hazard ratio</th>
<th>P-value</th>
<th>Survival advantage</th>
</tr>
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<tbody>
<tr>
<td>GOG 218 [7]</td>
<td>Arm 1: carboplatin + paclitaxel + placebo</td>
<td>625</td>
<td>10.3 (12.0α)</td>
<td>0.91</td>
<td>0.16</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Arm 2: carboplatin + paclitaxel + bevocuzumab + placebo</td>
<td>623</td>
<td>11.2</td>
<td>0.81</td>
<td>&lt;0.0001</td>
<td>Stage IV</td>
</tr>
<tr>
<td></td>
<td>Arm 3: carboplatin + paclitaxel + bevocuzumab with maintenance (total 15 months)</td>
<td>625</td>
<td>14.1 (18.0α)</td>
<td>0.65α</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>ICON7 [8]</td>
<td>Arm 1: carboplatin + paclitaxel</td>
<td>764</td>
<td>17.3α</td>
<td>0.72</td>
<td>&lt;0.0001α</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arm 2: carboplatin + paclitaxel + bevocuzumab with maintenance (total 12 months)</td>
<td>764</td>
<td>19.0α</td>
<td>0.65α</td>
<td>&lt;0.0001α</td>
<td></td>
</tr>
<tr>
<td>AURELIA [9]</td>
<td>Arm 1: chemotherapy*</td>
<td>182</td>
<td>3.4α</td>
<td>0.48</td>
<td>0.001</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Arm 2: chemotherapy** + bevocuzumab</td>
<td>179</td>
<td>6.7α</td>
<td>0.48</td>
<td>0.001</td>
<td>No</td>
</tr>
<tr>
<td>OCEANS [10]</td>
<td>Arm 1: carboplatin + gemcitabine + placebo</td>
<td>242</td>
<td>8.4α</td>
<td>0.48</td>
<td>&lt;0.0001</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Arm 2: carboplatin + gemcitabine + bevocuzumab until progression</td>
<td>242</td>
<td>12.4α</td>
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</tr>
</tbody>
</table>

PFS, progression-free survival; α, increased CA125 levels censored; α, Response Evaluation Criteria In Solid Tumors (RECIST); *, weekly paclitaxel, topotecan, or pegylated liposomal doxorubicin.
disease (AURELIA, from 3.4 to 6.7 months). It is important to note that the duration of bevacizumab in the two front-line studies was for a defined period of time compared with the studies in recurrent disease, where bevacizumab was administered until progression. The question of how prolonging bevacizumab treatment may benefit patients treated with first-line is currently under investigation.

HRs have the advantage of comparing the Kaplan–Meier curves globally instead of at median points, and analyses of HRs suggest an even greater benefit of adding bevacizumab to chemotherapy at relapse rather than at first-line. The HRs were 0.71 and 0.81 for GOG 218 and ICON7, respectively, in first-line and 0.48 for both the OCEANS and AURELIA trials in relapse. The weight placed on the PFS HR versus the absolute increase in months depends on one’s perspective, although patients probably relate more to prolonged tumor control measured in months. Thus, the choice of adding bevacizumab to either front-line or relapse is heavily dependent on factors other than PFS, such as OS and quality of life (QOL). One thing is clear; however, the addition of bevacizumab to chemotherapy prolongs disease control in EOC both in first-line and in relapse.

**side-effects and toxicity of bevacizumab in ovarian cancer**

*is the side-effect profile different if bevacizumab is offered to patients in first line rather than in relapse?*

Importantly, there has been concern about toxicity, especially bowel perforation [13], renal dysfunction, and hypertension [14] associated with the use of bevacizumab in all solid tumors in general, and EOC in particular. In addition, biomarkers and imaging have not consistently been predictive of response [14]. Importantly, both AURELIA and ICON7 were not placebo-controlled trials, creating a potential bias in evaluating efficacy and toxicity.

Table 2 summarizes the toxicities of interest observed in the four randomized EOC bevacizumab trials. The principal toxicities observed during bevacizumab treatment only vary slightly according to the treatment setting. There was a small increase in ‘gastrointestinal (GI) events’ in the AURELIA trial (4.4%) [9] and an unexpected high incidence of grade ≥3 proteinuria and bleeding in the OCEANS trial [10]. It is noteworthy that, in both recurrent disease trials, patients were treated with bevacizumab until progression, whereas in the two front-line studies (GOG 218 and ICON7) women were treated with bevacizumab for defined maximal periods, 15 and 12 months, respectively [7, 8]. This difference in the treatment duration may account for the slightly higher toxicity profile associated with bevacizumab use in relapse. In one phase II trial of single-agent bevacizumab, which allowed up to three prior lines of chemotherapy, the rate of bowel perforation was 11% [17]. This suggests that the number of prior treatment regimens could be a predictor of bevacizumab-associated GI adverse events (AEs). It is also possible that other selection factors, such as symptoms/signs of intestinal obstruction, evidence of intestinal tract involvement on imaging or rectal involvement on examination may be also be important in predicting ‘GI events’, such as perforations or fistulae.

**Table 2.** Toxicity of interest during bevacizumab treatment in first-line (GOG 218 and ICON7 trials) and in relapse (OCEANS and AURELIA trials)

<table>
<thead>
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<tbody>
<tr>
<td>GI events</td>
<td>2.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.4&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22.9 (grade ≥2)</td>
<td>18 (grade ≥3)</td>
<td>20 (grade ≥2)</td>
<td>17.4 (grade ≥3)</td>
</tr>
<tr>
<td>Proteinuria (grade ≥3)</td>
<td>1.6</td>
<td>&lt;1</td>
<td>1.7</td>
<td>8.5</td>
</tr>
<tr>
<td>Thromboembolic event&lt;sup&gt;e&lt;/sup&gt;</td>
<td>7.4</td>
<td>8</td>
<td>5.0</td>
<td>6.8</td>
</tr>
<tr>
<td>Bleeding (grade ≥3)</td>
<td>2.4</td>
<td>1</td>
<td>1.1</td>
<td>6.5</td>
</tr>
<tr>
<td>PRES</td>
<td>0.2</td>
<td>0</td>
<td>0.6</td>
<td>1</td>
</tr>
</tbody>
</table>

<sup>a</sup>Perforation, fistula, necrosis, and leak grade ≥2.

<sup>b</sup>Perforation, fistula, abscess, and wound-healing complications grade ≥3.

<sup>c</sup>Perforation and fistula/abcess grade ≥2.

<sup>d</sup>Perforation, fistula, and abscess all grades, wound-healing complications grade ≥3.

<sup>e</sup>Arterial any grade, venous grade ≥3.

PRES, posterior reversible encephalopathy syndrome.

**patient-reported outcomes (PROs) associated with the use of bevacizumab in ovarian cancer**

*do PROs differ according to bevacizumab use in the first-line rather than in the relapse setting?*

Because bevacizumab may be associated with serious toxicities that can occasionally be life threatening, QOL becomes a major consideration in treatment choice when differences in OS are small (or even nonexistent) and when treatments are expensive. Thus, PROs have influenced the adoption of bevacizumab in EOC. Unfortunately, OCEANS did not study PROs [10]. ICON7 and AURELIA were not placebo-controlled trials [9, 10] in contrast to GOG 218. The effect of a placebo on PROs is unknown. On the one side, placebo infusions can adversely impact QOL even though overt treatment-related AEs are lacking. Going to the infusion center for placebo infusions impacts patients’ lives. Conversely, open-label trials introduce a bias as clinicians and patients attribute changes in QOL to a known intervention.
Table 3. Patient-reported outcomes assessing quality of life from GOG 218, ICON7, and AURELIA

<table>
<thead>
<tr>
<th>Study</th>
<th>PRO instrument</th>
<th>Timing of assessments</th>
<th>Compliance (%)</th>
<th>Findings</th>
<th>P-value</th>
<th>Clinically meaningful?</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 218 [7, 18]</td>
<td>FACT-O TOI</td>
<td>Before cycles 1, 4, 7, 13, and 21; and 6 months after completing study therapy</td>
<td>74</td>
<td>Higher in arm 1 (placebo)</td>
<td>&lt;0.001</td>
<td>No: approximately three points mainly at cycle 4</td>
</tr>
<tr>
<td>ICON7 [8, 19]</td>
<td>EORTC QLQ-30</td>
<td>Primary end point: week 54</td>
<td>51</td>
<td>Higher in standard chemotherapy arm</td>
<td>&lt;0.001</td>
<td>Yes: 6.4 points</td>
</tr>
<tr>
<td>AURELIA [9, 20]</td>
<td>EORTC QLQ-30</td>
<td>Primary end point: EORTC QLQ-OV28 At week 8/9</td>
<td>67</td>
<td>Higher in bevacizumab arm</td>
<td>0.002</td>
<td>Yes: 6.4 points</td>
</tr>
</tbody>
</table>


All cross-trial comparisons are fraught with hazard, but this is especially true in the evaluation of PROs, since QOL end points, PRO instruments, and the timing of PRO evaluations frequently vary among studies. Finally, because subjects were enrolled on GOG 218 and ICON7 after bulk-reducing surgery, and frontline chemotherapy has a higher response rate compared with relapse, those treated at recurrence generally have bulkier disease and consequently more cancer-related symptoms than front-line patients who are generally asymptomatic. For example, front-line randomized bevacizumab EOC studies (GOG 218 and ICON7) included those with smaller volume disease and little or no ascites. Therefore, these studies mostly assessed the impact of bevacizumab-related toxicities on overall QOL, whereas AURELIA focused more on evaluating the impact of bevacizumab on QOL associated with disease-related symptoms. Table 3 summarizes the PROs of GOG 218 [18], ICON7 [19], and AURELIA [20]. When disease-related symptoms were minimal, such as in GOG 218 and ICON7, bevacizumab-related toxicities caused only a small decrease in QOL. Alternatively, when disease-related symptoms were present due to recurrent EOC (AURELIA), the added clinical activity of bevacizumab helped ameliorate symptoms such as those associated with ascites. Unfortunately, QOL was not measured beyond progression. Thus, the potential bevacizumab QOL benefit in delaying relapse and subsequent therapies might not be adequately captured in the absence of data evaluating QOL relative differences in remaining on bevacizumab, compared with receiving conventional second-line therapy.

**other factors in considering treatment in the front-line versus recurrent disease setting**

Treatment benefit must also be evaluated in relationship with treatment duration: does the ratio of disease control (PFS) prolongation/duration of treatment prolongation with bevacizumab maintenance therapy favor the use of bevacizumab in first-line?

To evaluate the entire disease control benefit of a new treatment, associated monetary costs must be considered. In EOC, the financial ramifications of bevacizumab are primarily related to the cost of the drug and its administration. This is impacted by the duration of therapy. Other factors to consider include the length of time without treatment and disease-related symptoms as well as the cost of AEs. These uncertainties have created much controversy [21].

In an attempt to measure the treatment burden versus the benefit, one can calculate the ratio of bevacizumab maintenance treatment length/additional PFS length achieved with bevacizumab therapy added to chemotherapy, compared with chemotherapy alone. For instance, the median time of maintenance bevacizumab treatment is equal to the median PFS of 14.1 months in GOG 218 (shorter than the planned 15 months of treatment) to which one subtracts the chemotherapy treatment length arbitrary fixed at 5 months (median of six cycles) for a median maintenance treatment estimated of 9.1 months. The associated PFS advantage for bevacizumab has been reported to be 3.8 months in this trial. Thus, the ratio of the length of maintenance bevacizumab to PFS bevacizumab benefit is 2.39. This ratio means that patients in GOG 218 were treated 2.39 months by bevacizumab to get a PFS benefit of 1 month. This ratio is 4.7 for ICON7, 1.85 and 0.52 for OCEANS and AURELIA, respectively. Thus, the ratio between the gain in disease control length and the length of additional treatment with bevacizumab maintenance required to obtain this benefit favors bevacizumab treatment at relapse. This analysis is not definitive, but is hypothesis generating and provocative.

**using bevacizumab after prior bevacizumab**

Finally, there is evidence that bevacizumab can be used across multiple lines of therapy in individual patients, so that use in the front-line setting does not preclude a potential benefit in the recurrent disease setting [22]. In fact, re-treatment with bevacizumab in patients with metastatic colorectal cancer has been shown to prolong survival by 19%, for a median of 1.4 months compared with a strategy of chemotherapy alone after progression on first-line bevacizumab ($P=0.0062$) [23]. The use of bevacizumab after bevacizumab in EOC is currently tested in a randomized trial, but if bevacizumab is to be used in
multiple lines of therapy, the debate of front-line versus relapse use is moot.

unanswered questions

Many other questions regarding the use of bevacizumab in EOC remain unanswered. The four positive randomized phase III trials ask more questions than they answer. The only definitive trial is a negative one. For example, should bevacizumab be used alone or in combination? Single-agent use is clearly less toxic, making single-agent maintenance therapy with bevacizumab as part of front-line treatment attractive [1]. A single-agent bevacizumab arm is glaringly missing from AURELIA. One thing is clear; though the duration of bevacizumab matters. Longer treatment is associated with a greater clinical benefit at the risk of more expense and maybe even toxicity. Trials are ongoing evaluating longer periods of treatment in first-line therapy (BOOST AGO-OVAR 17—NCT01462890, evaluating 15 versus 30 months of bevacizumab treatment) or in relapse after first-line treatment (ENGOT—ov17/MITO16 trial). Other unanswered questions include: what is the role of bevacizumab in intraperitoneal chemotherapy and dose-dense chemotherapy (e.g. weekly paclitaxel)? What is the optimal dose of bevacizumab? How does bevacizumab compare with oral anti-VEGF agents as well as non-VEGF angiogenesis compounds? Novel combinations of bevacizumab are also being investigated. Finally, there may be subsets of patients that stand to benefit most to bevacizumab or be refractory based on host or tumor biology. This is also an active area of research.

In summary, the choice of using bevacizumab in the upfront treatment of EOC or at the time of recurrence should be based on the relative efficacy and safety as well as cost. Bevacizumab fulfills the treatment objectives in patients with EOC both in front line and in relapse. The impressive PFS HRs for AURELIA and OCEANS (0.48) and the QOL improvement in AURELIA bring compelling evidence that adding bevacizumab to chemotherapy in relapse is associated with a significant clinical benefit. Perhaps, front-line bevacizumab is slightly safer. The OS advantage in stage IV patients in GOG 218 and those at highest risk of recurrence in ICON7 is consistent with the hope that bevacizumab can increase the cure rate in a subset of patients with EOC. In this respect, one should be tempted to preferentially use bevacizumab at the time of first-line therapy. Appropriately designed and executed randomized studies comparing this active agent in front-line with recurrence are needed. More importantly, multiple lines of bevacizumab therapy should be studied.

acknowledgements

The authors would like to thank Daniele Sumner and Adriana Rojo for their administrative assistance in submission of the manuscript.

disclosure

All the three authors have received research funding and honoraria from F. Hoffmann-La Roche Ltd.

references

20. Stockler MR, Hilpert F, Friedlander M et al. AURELIA Investigators. Health-related quality of life (HRQoL) results from the AURELIA trial evaluating bevacizumab (BEV) plus chemotherapy (CT) for platinum-resistant recurrent ovarian cancer (OC). J Clin Oncol 2013; 31(15 Suppl, Gynecol Oncol Section); abstr 5542.
