Editorial

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Bevacizumab and oral metronomic cyclophosphamide in platinum-resistant ovarian cancer

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Ovarian cancer presents at advanced stage in around 75% of the affected patients. Despite improvements in treatments, the 5-year survival rate remains poor. Over 70% of patients with advanced ovarian cancer will relapse and despite a good chance of remission from further chemotherapy, patients eventually become resistant to cytotoxic agents. Efficient alternatives to chemotherapy are thus urgently needed.

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that targets vascular endothelial growth factor-A. As a single-agent drug, it has shown response rates of 16%–21% in the treatment of recurrent ovarian cancer. Four phase III randomized trials have been reported evaluating the addition of bevacizumab to standard chemotherapy as front-line treatment or in the recurrent setting of advanced ovarian cancer [1-4]. All these trials showed a statistically significant improvement in progression-free survival (PFS), although no improvement in overall survival has yet been reported, except in some subset of patients. The main adverse event is hypertension. Other serious, but uncommon adverse events include gastrointestinal perforation as well as renal or vascular toxicity. Overall, bevacizumab is the first biological therapy to have shown efficacy in ovarian cancer and to obtain approval in certain countries. In this issue, Barber et al. [5] reported 42.4% of an impressive overall response rate, including 10.6% of complete response rate in 66 patients with heavily pre-treated recurrent platinum-resistant ovarian cancer when they were offered a combination of bevacizumab and oral metronomic cyclophosphamide (OMC). Despite this remarkable tumor shrinkage activity, the median PFS remained relatively short, between 3 months for the whole population and 5 months for the responders. However, this modest duration of disease control has to be put in the context of women who had received previously a median of 6.5 lines of chemotherapy. The results reported in this study are in line with those previously reported in similar retrospective studies of heavily pre-treated ovarian cancer patients treated with bevacizumab and OMC with a 40%–53% of response rate and 3.9–5.5 months of PFS. Adverse events were those expected with bevacizumab treatment and only one patient suffered from bowel perforation. Unfortunately, because it is a retrospective study, patient-reported outcomes such as quality of life and control of patient symptoms, which are considered as important objectives of treatment in recurrent platinum-resistant ovarian cancer, were not captured.

The substantial activity of the bevacizumab-OMC combination observed in this series of patients addresses the question of bevacizumab synergy with chemotherapy in general, and OMC in particular, in the recurrent ovarian cancer setting. To our knowledge, there is no randomized study comparing the combination of chemotherapy plus bevacizumab vs. bevacizumab alone. The AURELIA trial, however, has compared prospectively the combination of chemotherapy plus bevacizumab versus chemotherapy alone in patients with platinum-resistant ovarian cancer pre-treated with one or a maximum of 2 previous lines [4]. Chemotherapy was a single agent therapy at investigators' choice, either weekly paclitaxel or pegylated liposomal doxorubicin or topotecan. The adding of bevacizumab to chemotherapy significantly increased the

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chemotherapy response rate from 12% to 27% (p=0.001) and PFS from 3.4 to 6.7 months (hazard ratio, 0.48; p<0.001) suggesting synergy between bevacizumab and chemotherapy.

To explain this synergy with cytotoxic drugs, vessel normalization is considered as the main mechanism of bevacizumab action. Vessel normalization is promoted by the decreased intra-tumor interstitial pressure due to the decrease in vascular permeability by anti-vascular endothelial growth factor (VEGF) therapy [6]. By this mechanism, bevacizumab is supposed to increase the amount of the chemotherapeutic agent that reaches the tumor.

But why, among the variety of active cytotoxic drugs in ovarian cancer, OMC might be an agent of choice to combine with bevacizumab? We know that OMC has anti-tumor activity by itself in ovarian cancer [7]. The main primary target of OMC is thought to be the tumor's neovasculature. Thus OMC and the anti-VEGF bevacizumab could be synergistic in their anti-angiogenic effect. In the AURELIA trial, the most impressive results are observed with the combination of weekly paclitaxel and bevacizumab (response rate, 51.7%; median PFS, 10.4 months). The explanation for this observation is the synergistic activity of bevacizumab and the anti-angiogenic property of paclitaxel when administered as a weekly schedule. However, OMC does not only reduce angiogenesis. It has also been shown to decrease CD133+/CD44+/CD24+ cancer stem cells [8]. Perhaps even more importantly, OMC and bevacizumab may have a synergistic effect on tumor response by the immune system. OMC is well known to impact on T regulatory cells, which inactivate effector T cells. And, tumor-infiltrating T cells have been associated with improved outcome in ovarian cancer. In addition, we can hypothesize that vessel normalization induced by bevacizumab could also facilitates the effector T cell homing. Thus, the combination of OMC with bevacizumab could attenuate two important immune-evading mechanisms of tumor, leading to the activation of antitumor immunity [9].

However, the encouraging data observed with the combination of bevacizumab and OMC in retrospective series of heavily pre-treated ovarian cancer patients have been reproduced neither in prospective trials nor in patients at earlier stage of the disease. Among the 70 patients with recurrent ovarian cancer treated with this combination prospectively by Garcia et al. [10], 28 were platinum-resistant and they achieved a disappointing response rate of 12% with a median PFS shorter than 5 months. The discrepancy between these results and those of this study might be due to the difference of methodology as usually observed between retrospective and prospective studies. However, it might be due to the time in the disease evolution when the combination was administered. In the trial run by Garcia et al. [10], patients had received a maximum of 3 prior regimens in contrast to a median 6.5 in the series of Barber et al. [5]. It has been noticed that the hazard ratio of bevacizumab activity in combination with chemotherapy followed by maintenance may be different according to the disease setting, suggesting a higher efficacy of bevacizumab in relapse than in first-line. This difference might be due to insufficient duration of treatment in first-line justifying the on-going BOOST trial comparing 15 months vs. 30 months of bevacizumab treatment after initial debulking surgery. Another hypothesis would be that bevacizumab activity increases with tumor size and presence of aberrant vasculature. In this case, the combination of OMC and bevacizumab could be an attractive treatment to explore in patients with significant burden of disease (without bowel involvement) and correlative intratumoral immunosuppression.

In conclusion, there is a strong rationale for combining oral metronomic cyclophosphamide and bevacizumab in recurrent platinum-resistant ovarian cancer. The accumulation of data should prompt future prospective trials comparing this combination with weekly paclitaxel and bevacizumab, the current most attractive combination in this setting.

CONFLICT OF INTEREST

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

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