Correspondence

J Gynecol Oncol Vol. 25, No. 4:355-356
http://dx.doi.org/10.3802/jgo.2014.25.4.355
pISSN 2005-0380 · eISSN 2005-0399

Journal of Gynecologic Oncology
jgo

Bevacizumab in combination with gemcitabine and carboplatin in recurrent ovarian cancer: a critical consideration

To the editor: Recently, Aghajanian et al. [1] have published the results of the independent radiologic review concerning the OCEANS trial [2]. This study, published in 2012, compared the combination gemcitabine-carboplatin (GC) plus bevacizumab (BV), including BV until progression; versus GC plus placebo in the treatment of recurrent platinum sensitive ovarian cancer (recurrence >6 months after completion of front-line platinum based chemotherapy). The review confirmed the results reported in OCEANS trial, with the achievement of the primary endpoint. In fact, it demonstrated a statistically significant advantage in progression-free survival (PFS) for the experimental arm with GC+BV (hazard ratio [HR], 0.451; 95% confidence interval [CI], 0.351 to 0.580; p<0.001).

In OCEANS trial, the median PFS was 12.4 months versus 8.4 months (p<0.001) in the GC+BV arm than in the placebo arm. The advantage was 4 months for the experimental arm [2]. As reported by the authors, the OCEANS trial is the first positive, randomized, phase III trial evaluating the addition of a biologic therapy to a standard platinum doublet in recurrent ovarian cancer. The platinum doublet therapy including GC was chosen, as explained by the authors, based on AGO-OVAR-NCIC-EORTC phase III study published in 2006 by Pfisterer et al. [3]. This study reported a statistically significant improvement in PFS for GC compared with carboplatin alone. The median PFS for the experimental arm was 8.6 months versus 5.8 months for the control arm (HR, 0.72; 95% CI, 0.58 to 0.90; p=0.003).

We know that this regimen is one of the treatment options in recurrent platinum sensitive ovarian cancer, however we don't think it could be consider the standard of treatment. Analyzing the results of the "historical" trials concerning the platinum doublet therapy versus carboplatin alone in recurrent platinum sensitive ovarian cancer (**Table 1**), we can observe that the combinations carboplatin-paclitaxel as well as carboplatin-pegylated liposomal doxorubicin (PLD) give a statistically significant advantage in PFS of about 3 to 4 months (depending from the trial). The median PFS for the combination arms is 12 months [4,5].

Although it's not possible to directly compare different studies, it's important to underline that the median PFS of experimental arms from these trials, including platinum doublets versus carboplatin, are similar to the PFS registered in the GC+BV arm in the OCEANS study. So GC combination seems to be inferior compared to other regimens versus carboplatin alone. In OCEANS trial GC+BV plus BV maintenance versus GC+placebo the PFS was 12.4 versus 8.4, respectively. In previous reported historical data the PFS with platinum doublet regimens, as already noted, is of about 12 months.

So, considering PFS as well as overall survival results (**Table 1**), we think that the choice of GC combination in OCEANS trial maybe was not the best selection. BV has economical as well as safety implications (serious adverse events occurred in 34.8% of patients in BV arm), so we should consider when it can be really useful in improving patients' outcome.

We think that probably other combinations could be more effective in improving PFS in recurrent platinum sensitive ovarian cancer. Moreover, as already reported by Tomao et al. [6], we agree about the doubt concerning the lack of CA-125 evaluation to assess progression disease. We think that marker evaluation in recurrent ovarian cancer, as indicated in previous studies and by the Gynecologic Cancer Intergroup, is essential in the management of recurrent ovarian cancer, especially in trials including maintenance therapy. Assessing progression disease only with radiological/response evaluation criteria in solid tumors (RECIST) criteria is debatable.

Our doubts about OCEANS trial results are confirmed in National Comprehensive Cancer Network American guidelines, version 2.2014. In fact, the combination GC+BV is a category 2B recommendation (that means "based upon lower-level evidence"). As reported in guidelines, this is because there is less consensus among the NCCN panel that this intervention is appropriate. Panel members fell other combination regimens are more beneficial and effective than those with BV.

We know that European Medicines Agency approved the combination GC+BV in platinum sensitive relapsed ovarian cancer in patients who have not previously received BV. According to previous considerations we express some doubts about the effectiveness of this regimen or better we believe

Table 1. Phase III trials. Recurrent platinum sensitive ovarian cancer

Trial	Chemotherapy	Progression-free survival (mo)		Overall survival (mo)	
		Median	p-value	Median	p-value
Pfisterer et al. [3], AGO/OVAR	CBDCA	5.8	0.031	17.3	0.73
	CBDCA+GEM	8.6		18	
Parmar et al. [4], ICON4	Platinum based	9	<0.001	24	0.023
	PTX+CBDCA	12		29	
Alberts et al. [5], SWOG	CBDCA	8	0.02	18	0.02
	CBDCA+PLD	12		26	

CBDCA, carboplatin; GEM, gemcitabine; PLD, pegylated liposomal doxorubicin; PTX, paclitaxel.

that more strong evidences about BV efficacy in this setting and about the best chemotherapy to combine with it should be provided.

Nowadays with the introduction of BV in front line therapy, we need further studies to define the better treatment option in platinum recurrent ovarian cancer, to define which patients could benefit from BV based therapy, and to choose the better strategy based on time of recurrence, considering new available options for platinum partially sensitive relapsed ovarian cancer patients [7].

CONFLICT OF INTEREST

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

REFERENCES

1. Aghajanian C, Goff B, Nycum LR, Wang Y, Husain A, Blank S. Independent radiologic review: bevacizumab in combination with gemcitabine and carboplatin in recurrent ovarian cancer. Gynecol Oncol 2014;133:105-10.
2. Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 2012;30:2039-45.
3. Pfisterer J, Plante M, Vergote I, du Bois A, Hirte H, Lacave AJ, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol 2006;24:4699-707.
4. Parmar MK, Ledermann JA, Colombo N, du Bois A, Delaloye JF, Kristensen GB, et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet 2003;361:2099-106.
5. Alberts DS, Liu PY, Wilczynski SP, Clouser MC, Lopez AM, Michelin DP, et al. Randomized trial of pegylated liposomal doxorubicin (PLD) plus carboplatin versus carboplatin in platinum-sensitive (PS) patients with recurrent epithelial ovarian or peritoneal carcinoma after failure of initial platinum-based chemotherapy (Southwest Oncology Group Protocol S0200). Gynecol Oncol 2008;108:90-4.
6. Tomao F, Tomao S, Panici PB. Improvement in progression-free survival in OCEANS bevacizumab arm: a critical point of view. J Clin Oncol 2013;31:166-7.
7. Sehouli J, Alfaro V, Gonzalez-Martin A. Trabectedin plus pegylated liposomal doxorubicin in the treatment of patients with partially platinum-sensitive ovarian cancer: current evidence and future perspectives. Ann Oncol 2012;23:556-62.

Sara Giovannoni, Patrizia Trenta

Oncology Unit B, Department of Radiology, Oncology and Human Pathology, Policlinico Umberto I, Sapienza University Rome, Rome, Italy

Correspondence to Sara Giovannoni
Oncology Unit B, Department of Radiology, Oncology and Human Pathology; Policlinico Umberto I, Sapienza University Rome, Viale Regina Elena 324, 00161 Rome, Italy. E-mail: sagiovannoni@gmail.com

http://dx.doi.org/10.3802/jgo.2014.25.4.355