



REBECA trial: a new piece of the evidence for bevacizumab in platinum-resistant recurrent ovarian cancer

Daniele Lavacchi¹, Sara Fancelli¹, Marta Rita Gatta Michelet¹, Martina Catalano¹, Giandomenico Roviello²

¹School of Human Health Sciences, ²Department of Health Sciences, University of Florence, Florence, Italy

Correspondence to: Giandomenico Roviello, MD, PhD. Department of Health Sciences, University of Florence, Viale Pieraccini, 6, 50139, Florence, Italy. Email: giandomenicoroviello@gmail.com.

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Lee *et al.* (1) evaluated the efficacy and safety of bevacizumab in combination with single-agent chemotherapy for platinum-resistant ovarian cancer in a large retrospective analysis involving Korean women with platinum-resistant recurrent ovarian cancer from 27 different institutions. All evaluated patients had a platinum-resistant recurrent ovarian cancer treated with a single-agent chemotherapy in combination with bevacizumab, independently chose by the investigators, after progression from one or two lines of previous therapies. The chemotherapy included weekly paclitaxel, topotecan, or pegylated liposomal doxorubicin. The primary endpoint was progression free survival (PFS), the secondary endpoints were overall response rate (ORR); PFS2 (calculated as the time from the start of chemotherapy to the occurrence of objective disease progression on next-line therapy or death from any cause), overall survival (OS) and safety/tolerability. From August 2015 to August 2017, a total of 391 women were retrospectively evaluated. Two hundred and fifty-nine (66.2%) received bevacizumab with pegylated liposomal doxorubicin, 94 (24.0%) with topotecan, and 38 (9.7%) with weekly paclitaxel. The median duration of treatment was more than one year (13.6 months; range, 1–45 months) for the entire population. In this study, ORR was 32.9% (31.3% in second-line therapy and 34.9% in third-line therapy). In subgroup analysis, the ORR was significantly higher only for the weekly paclitaxel group compared with pegylated liposomal doxorubicin group (48.6% versus 30.6%, $P=0.008$). The median PFS of the overall population was 6.1 months with the longer value for the weekly paclitaxel cohort. Median OS was 22 months for the entire population with a significant advantage in

OS for the topotecan cohort compared with the pegylated liposomal doxorubicin cohort ($P=0.018$). Regarding safety, the rate of adverse events from bevacizumab were in line with those usually reported (2) while the pegylated liposomal doxorubicin cohort had fewer grade ≥ 3 adverse events however, only the 7.4% of all patients discontinued treatment because of adverse events from bevacizumab-containing regimens. The authors concluded that the safety and effectiveness of chemotherapy with bevacizumab in Korean platinum resistant ovarian cancer patients were consistent with previous experiences (1).

To date, the treatment of patients with platinum-resistant ovarian cancer is challenging and often unsuccessful. Several phase 2 trial have explored the efficacy of bevacizumab in combination with chemotherapy, showing promising rates of response and encouraging survival outcomes (3). The only randomized phase 3 study was AURELIA, which demonstrated a statistically significant benefit in terms of PFS (primary endpoint) and ORR from the addition of bevacizumab to chemotherapy (pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan). PFS and ORR were 6.7 months and 27.3% in patients treated with bevacizumab plus chemotherapy compared with 3.4 months and 11.8% in patients treated with chemotherapy alone (PFS HR 0.48, $P<0.001$). Nevertheless, one of the main factor that has limited the applicability of AURELIA trial was that a statistically significant difference in OS was not achieved. In platinum-resistant patients, usually associated with a poor prognosis and with few therapeutic options, survival should remain one of the most important endpoints for clinical trials, although the OS benefit is regularly underestimated

due to cross over (40% in AURELIA trial) (4). However, an exploratory analysis of the AURELIA trial supported the efficacy of bevacizumab in terms of OS in platinum-resistant patients. In this analysis, a survival benefit was observed in patients who received bevacizumab upfront or at crossover compared to those who never received bevacizumab (5).

Targeting tumor angiogenesis, bevacizumab remains an effective option for the treatment of patients with advanced ovarian cancer (2). However, reliable predictive biomarkers for bevacizumab had not yet been identified. Despite recent advances in molecular genome sequencing as a support to therapeutic choices, it remains unclear whether it is better to adopt a molecular or clinical selection of patients. For this purpose, a whole genome gene expression analysis in a subset of patients treated with bevacizumab within ICON7 trial showed a remarkable PFS benefit offered by the use of bevacizumab in patients with proliferative tumors (HR 0.55, $P=0.016$) compared with mesenchymal (HR 0.78, $P=0.41$), immunoreactive (HR 0.67, $P=0.08$), or differentiated tumor (HR 0.85, $P=0.61$) (6).

The treatment of ovarian cancer has undergone remarkable changes also with the introduction of poly-(ADP-ribose) polymerase (PARP) inhibitors. However, if in BRCA-mutated, platinum-sensitive patients the disease control rate (DCR) was 69–81%, it drops to 39–45% in platinum-resistant and 23–29% in platinum-refractory patients (7,8). In addition, several trials have explored combination treatments such as anti-PD-1/PD-L1 monoclonal antibodies (MoAbs) with PARP inhibitor, anti-angiogenic agents, or chemotherapy (9–11). In a recent phases 1 and 2 trial, niraparib in combination with pembrolizumab, (anti-PD-1 MoAb) demonstrated a promising activity in patients with recurrent platinum-resistant ovarian cancer, with ORR of 18% and DCR of 65%. Similar rates of response were observed in patients who had previously received bevacizumab or had not, and across subgroups based on BRCA or homologous recombination deficiency (HRD) status (9). The combination of nivolumab (anti-PD-1 MoAb) and bevacizumab was evaluated in a phase 2 trial for patients with relapsed ovarian cancer. The activity of this combination was greater in patients with platinum-sensitive than in platinum-resistant cancer, with ORR of 40.0% and 16.7%, respectively (10). Moreover, in the randomized phase 3 JAVELIN Ovarian 200 trial, the combination of avelumab (anti-PD-L1 MoAb) and pegylated liposomal doxorubicin demonstrated a modest activity in patients with platinum-resistant or refractory

ovarian cancer, with ORR of 13.3% (11).

In conclusion, REBECA trial evaluated the efficacy and safety of bevacizumab with single-agent chemotherapy chosen by the investigators in Korean patients with platinum-resistant ovarian cancer. Several limitations deserve specific attention, mainly due to the intrinsic nature of an observational study. The lack of a control group, the choice of the chemotherapeutic agent based on the preferences of the investigators, the lack of stratification and exploratory analysis of predictive biomarkers represented the major limitations that profoundly affect the strength of the conclusions. In addition, the participation of exclusively Korean centers precludes a comprehensive evaluation of efficacy and tolerability in both Western and Eastern patients. However, this study offers an additional evidence on the use of bevacizumab in routine clinical practice for this subset of patients with ovarian cancer who have few treatment options.

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