ToleRability of BevacizUmb in elderly Ovarian cancer patients (TURBO study): a case-control study of a real-life experience.

G. Amadio, C. Marchetti, E.R. Villani[^], D. Fusco[^], F. Stollagli, C. Bottoni, M. Distefano, G. Colloca[§], G. Scambia^{*}, A. Fagotti^{*}

Division of Gynecologic Oncology, Fondazione Policlinico Universitario A. Gemelli, IRCCS

[^]Division of Geriatrics, Fondazione Policlinico Universitario A. Gemelli, IRCCS

[§]Division of Radiology, Radiotherapy and Hematology, Fondazione Policlinico Universitario A. Gemelli, IRCCS

^{*}Catholic University Sacred Heart, Rome, Italy

Objective. Bevacizumab maintenance following platinum-based chemotherapy is an effective treatment for epithelial ovarian cancer (EOC), both in primary and recurrent disease. Our aim was to identify criteria to select elderly patients who can safely benefit from bevacizumab addition.

Methods. This is a case-control study on patients with primary or recurrent EOC who received platinum-based chemotherapy plus bevacizumab, between January 2015 - December 2016. Patient characteristics, treatment details and adverse events were reviewed and analyzed in two setting: younger (<65 years, group 1) and elderly (≥65 years, group 2). A binary logistic model was applied to correlate clinical variables and severe (grade ≥3) toxicity risk.

Results. Overall, 283 patients with EOC were included, with 72 (25.4%) older patients compared with 211 (74.6%) younger women. Bevacizumab had been administered to 234 patients (82.7%) as first-line treatment and in 49 (17.3%) with recurrent disease. At diagnosis, elderly patients presented with at least one comorbidity and were taking at least 1 medication in 84.7% and 80.6% of the cases

respectively, compared with correspondingly 47.4% and 37.4% in group 1 (p<0.001). Nonetheless, the occurrence of serous (G3/G4) adverse events did not increase among the older group. Creatinine serum levels > 1.1 g/dl, estimated glomerular filtration rate (eGFR) < 60 ml/min, ≥ 3 comorbidities were independently associated with a higher severe toxicity. A decision tree algorithm has been proposed for the entire population Creatinine level and comorbidities were of relative importance to predict severe toxicity in OC patients who received platinum-based chemotherapy plus bevacizumab. Details are shown in Figure 1. Patients were partitioned in three groups: i) patients with creatinine level < 0.99 (6% probability of severe toxicity); ii) patients who had creatinine level ≥ 0.99 and comorbidities ≥ 4 (100% probability of severe toxicity); iii) patients who had creatinine level ≥ 0.99 and comorbidities < 4 (71% severe toxicity probability).

Conclusions. Elderly patients with EOC can safely be treated with bevacizumab; factors other than age, as higher creatinine serum levels, eGFR and number of comorbidities should be considered to better estimate bevacizumab-related toxicity risk.

Table 1. Adverse events G3/G4 among patients and according to age.

Variable	All cases Nr (%)	Group 1 Age < 65 yr Nr (%)	Group 2 Age ≥ 65 yr Nr (%)	P value
Patients	283	211 (74.6)	72 (25.4)	-
Patients with Grade 3/4 AEs	27 (9.5)	19 (9.0)	8 (11.1)	0.599
BEV related G3/G4 AEs [^]	5 (1.97)	4 (1.9)	1 (1.4)	0.631
Hematologic	7 (2.4)	6 (2.8)	1 (1.4)	0.684
Gastrointestinal (bowel perforation, subocclusion, volvulus)	6 (2.1)	4 (1.9)	2 (2.8)	0.643
Venous thromboembolic events	1 (0.3)	1 (0.5)	0	0.748
Arterial thromboembolic events/stroke/ictus	6 (2.1)	5 (2.3)	1 (1.4)	0.530
Hypertension	8 (2.8)	4 (1.9)	4 (5.6)	0.112
Proteinuria	8 (2.8)	3 (1.4)	5 (7)	0.627
Cronic kydney failure	1 (0.3)	1 (0.4)	0	0.55
Bleeding	3(1)	2(0.9)	1 (1.4)	0.75
Wound Healing Complication	1 (0.3)	0	1 (1.4)	0.08
Fistula/abscess				
Congestive heart failure	0	0	0	NA
Posterior reversible encephalopathy syndrome	0	0	0	NA
Arthralgia	1 (0.3)	0	1 (1.4)	0.08
Liver (high liver enzymes)	1 (0.3)	1 (0.4)	0	0.55
Main reason for BEV discontinuation				
Disease progression	96 (34)	70 (33.1)	26 (36.1)	0.488
Treatment related AEs	17 (6)	10 (4.7)	7 (9.7)	0.355
Worsening comorbidity	0	0	0	/
Other	1 (0.3)	1 (0.5)	0	0.956

Table 2. Logistic regression of factors predictive of G3/G4 adverse events

Variable	OR	95% CI		P value
Age ≥ 65 ys	0.52	0.16	1.68	0.278
ECOG PS ≥ 1	2.18	0.50	9.47	0.298
Comorbidies number ≥ 3	6.60	1.87	23.36	0.003
Creatinine serum levels ≥ 1.1 mg/dL	12.68	2.92	55.07	0.001
eGFR CDK-EPI <60 ml/min	10.35	3.66	29.31	0.001
Polypharmacy	1.57	0.25	8.76	0.799

Figure 1. Classification tree for ovarian cancer patients who received platinum-based chemotherapy plus bevacizumab.