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BEVACIZUMAB AS MAINTENANCE TREATMENT IN PATIENTS WITH OVARIAN CANCER

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ABSTRACT
The article discusses the use of the drug bevacizumab in patients with ovarian cancer.
АННОТАЦИЯ
В статье рассматривается применение препарата бевацизумаб у больных раком яичников.
Key words: ovarian cancer, chemotherapy, bevacizumab.
Ключевые слова: рак яичников, химиотерапия, бевацизумаб.

In their recent article published in Journal of Clinical Oncology, Tewari et al highlighted that in the GOG0218 trial, neither first-line bevacizumab concurrent with chemotherapy nor bevacizumab concurrent with chemotherapy plus maintenance significantly improved overall survival (OS) compared with chemotherapy alone, even though bevacizumab administered throughout treatment has prolonged median progression-free survival (PFS) by approximately 4 months. Moreover, the authors demonstrated that germ line or somatic mutations in BRCA1/2 genes were prognostic, but not predictive, of bevacizumab efficacy.

However, the median OS for patients with BRCA mutations was the same in the control and maintenance bevacizumab arms (62.5 and 62.6 months, respectively), whereas in BRCA wild-type patients, bevacizumab led to a 3-month improvement in OS, although this was not statistically significant.[7] Again, maintenance bevacizumab led to a median PFS improvement only in patients without mutations (15.7 v 10.6 months; hazard ratio [HR], 0.71; 95% CI, 0.60 to 0.85; P 5 .0001), not in those with mutations (HR, 0.95; 95% CI, 0.71 to 1.26). [1-3] Similarly, in the AGOOVAR 16 phase III randomized trial of maintenance pazopanib versus placebo after first-line chemotherapy, a clinically meaningful difference in efficacy with pazopanib for PFS according to BRCA status was seen, with a median PFS significantly longer for the pazopanib arm versus placebo in BRCA wild-type patients (17.7 v 14.1 months; HR, 0.77; 95% CI, 0.62 to 0.97; P 5 .024); median PFS was not significantly different in those with BRCA mutations (30.2 v 30.3 months; HR, 1.36; 95% CI, 0.66 to 2.82; P 5 .41). [4]

In a recent phase II randomized trial in patients with platinum-sensitive relapsed ovarian cancer, [5] niraparib plus bevacizumab significantly prolonged the median PFS when compared with niraparib alone (11.9 v 5.5 months; HR, 0.35; 95% CI, 0.21 to 0.57; P .0001). This improvement was reported in BRCA wild-type patients (11.3 v 4.2 months; HR, 0.32; 95% CI, 0.17 to 0.58; P 5 .0001), but not in those with BRCA mutations (14.4 v 9.0 months; HR, 0.49; 95% CI, 0.21 to 1.15; P 5 .095), suggesting that BRCA-mutated tumors may not need the combination with bevacizumab.

A biologic explanation behind these findings could be related to the tumor microenvironment. Indeed, BRCA1 plays an important role in hypoxia-induced expression of VEGF, and less HIF-1 accumulates in hypoxic conditions in BRCA-deficient cells, but not in normoxic conditions or BRCA-proficient cells.6 Moreover, BRCA-disrupted tumors present more frequently an immunereactive subtype, with a higher presence of tumor-infiltrating lymphocytes (TILs), whereas a stromal or mesenchymal subtype expresses fewer immune cell genes and more angiogenesis-related genes [7]. Therefore, it could be hypothesized that bevacizumab is less active in BRCA-mutated ovarian cancer.

In this context, inflammation may play a fundamental role. Neutrophil-to-lymphocyte ratio (NLR) is one of the most widely used systemic inflammatory marker and is able to assess the balance between neutrophil dependent protumor inflammation and lymphocyte associated antitumor immune response, with a high NLR associated with poor survival in different treatments, including immune checkpoint inhibitors [8]. In a real-world retrospective study, we showed that a high NLR ($ 3) was associated with an improvement in median PFS and OS in patients with ovarian cancer treated with bevacizumab compared with controls, [9] and in a subanalysis, we recently observed an association between high NLR and BRCA wild-type status (82%). Moreover, a correlation between high TIL number and low NLR has been already demonstrated, [10] suggesting that in low immunereactive tumors, bevacizumab may increase the number of CD81 and CD41 T cells and reduce suppressive cytokines, tumor-infiltrating T-regulatory cells, and myeloid-derived suppressor cells, which ultimately could improve adaptive immunity. Inflammatory indexes such as NLR could serve as helpful predictive tools, when validated in prospective trials.

In their conclusions, the authors argued that PFS may have more clinically meaningful value, because the lack of improvement in OS may have been obscured by crossover and/or postprogression therapies. Such considerations led the authors to conclude that patients without contraindications may initiate bevacizumab while waiting for BRCA testing results, stating that

patients “with BRCA1/2 mutated carcinoma can be transitioned to maintenance olaparib, whereas those without mutations may remain on maintenance bevacizumab.”[7 p2326]

We have some concerns with these conclusions. The blinding of the treatment assignments after disease progression was contested; also, the primary end point of the GOG-0218 trial was modified from OS to PFS, and any other comparison became a secondary objective [2]. Moreover, the only arm that reached the primary end point in the study, resulting in a PFS improvement, was the arm receiving concurrent bevacizumab and chemotherapy plus maintenance, whereas results for the arm in which bevacizumab was stopped after chemotherapy did not differ from those for the control group [2]. Therefore, before incorporating bevacizumab into the treatment of patients with ovarian cancer, we suggest waiting for the results of BRCA testing.

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LEVERAGING CLINICAL TUMOR-PROFILING PROGRAMS TO ACHIEVE COMPREHENSIVE PRECISION CANCER MEDICINE

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УЛУЧШАЮЩИЕ КЛИНИЧЕСКИЕ ПРОГРАММЫ ПРОФИЛИРОВАНИЯ ОПУХОЛЕЙ ДЛЯ ДОСТИЖЕНИЯ МНОГОКРАТНОЙ ТОЧНОСТИ ОНКОЛОГИЧЕСКОЙ МЕДИЦИНЫ

ABSTRACT

The article is devoted to the use of clinical programs for profiling tumors in terms of improving the accuracy of cancer medicine.

АННОТАЦИЯ

Статья посвящена применению клинических программ профилирования опухолей с точки зрения повышения точности онкологической медицины.

Key words: clinical programs for tumor profiling, gremline, BRCA2, CHEK2, BRCA1.