Letter to the Editor

Dear Sir,

In spite of the limitations of conventional chemotherapy, the standard of care for women with advanced stage or poor-prognosis early stage ovarian cancer (OC) until 2011 was debulking surgery followed by adjuvant chemotherapy with a platinum agent and a taxane [1]. Although this approach still remains the mainstay of treatment, since then the use of anti-angiogenic agents in OC has moved from a theoretical concept to a key component of therapy. Bevacizumab has now been approved by the European Medicines Agency for use in combination with carboplatin and paclitaxel in newly-diagnosed OC, and by the US Food and Drug Administration for the treatment of platinum-resistant OC relapse. These approvals were mainly based on the results of four large-scale randomized trials, two conducted in the first-line settings (ICON-7 and GOG-218) and one each performed in platinum-sensitive and platinum-resistant OC relapse (OCEANS and AURELIA), which essentially showed an improvement in progression-free survival [2-5]. No overall survival (OS) benefit was observed initially, however a recent mature analysis of OS data from ICON-7 reported improved survival by subgrouping analysis, even if no survival benefit was noted when the overall study population was considered [6]. A number of retrospective studies are underway to identify predictive signatures, and several candidate tumor biomarkers have been analyzed, with some (e.g. microvessels density measured by CD31 staining) having promising clinical effects [7]. Also, two different molecular subtype classifications have been independently proposed, with one study identifying women with an immunological-active subtype for whom bevacizumab treatment would be detrimental [8] and another study identifying women with a mesenchymal-like subtype disease for whom bevacizumab treatment is beneficial [9]. Taken together, these findings appear to suggest that anti-angiogenic treatment could be effective in poor prognosis patients. However, a revision and an overall consensus on both the biomarker scoring system and molecular subtype classification are necessary because these were obtained by applying different methods of analysis/subtyping and evaluation criteria. Major limitations continue to be the complex and still unresolved biology underlying angiogenic processes and the intrinsic spatial and temporal molecular heterogeneity of OC, given that recent studies suggest that OC does not consist of mutually exclusive gene-expression subtypes but that individual tumors may instead express multiple overlapping subtype signatures [10].

These factors mean that clinicians now face the challenge of selecting the most appropriate first-line treatment for newly-diagnosed OC patients. However, questions relating to the prediction of patients who will benefit most and the optimum timing of therapy (at initial presentation, at recurrence or after development of platinum-resistance) remain unresolved, and need to be addressed to improve the cost-effectiveness of anti-angiogenic therapy by avoiding treatment of patients who stand to obtain little benefit.

Molecular subtyping systems essentially based on the gene expression profile have come to the OC setting relatively recently compared with other tumor

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types and, even if encouraging, they still have limited clinical application and utility. From this perspective, and considering the intrinsic heterogeneity in OC, revised patient stratification accounting for complex and diverse molecular features (miRNA-based expression signature, mutational signature, methylome profile) is expected to be more informative, possibly in association with tissue biomarker evaluation [11]. Also, first order patient stratification based on tumor at presentation has been shown to be insufficient; longitudinal sampling of tumor tissue at diagnosis, during treatment and at relapse is an alternative approach. Despite the many studies undertaken, no validated biomarkers for patient selection or response are currently available because all the above mentioned studies failed to provide conclusive results, and instead require robust independent validation. Longitudinal prospective studies, such as the MITO16/MANGO2a and MITO16/MANGO2b clinical trials, that have been designed to include translational endpoints with temporal multiple sampling might significantly contribute to addressing unresolved open questions about strategies for cost-effective treatment with bevacizumab.

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