Letter to the Editor

Dear Sir,

I read with great interest the "Breaking from the Lab" article by Birrer and colleagues, discussing state of the art of genetic profiling in ovarian cancer [1]. This comprehensive review highlights how molecular analyses have changed our way of thinking about epithelial ovarian cancer (EOC) and demonstrates that EOC is not a single disease but that different subtypes exist, not only based on the tumor histology but also on the expression of defined gene signatures.

In particular, a great effort has been made over the last few years to profile and characterize, from a molecular point of view, most common histotype of ovarian cancer – high-grade serous ovarian cancer (HGSOC) [2, 3]. As reported by Birrer et al., gene expression profiling certainly represents a powerful research tool that has made a huge contribution to the characterisation of HGSOC, but its implementation into clinical practice might be difficult [3]. Based on unsupervised clustering of gene expression, HGSOC can be consistently assigned to one of four different subgroups, displaying different prognostic and key biological features. However, most of the studies report that it is difficult to unambiguously assign a HGSOC patient to a single subtype [3]. Moreover, as has been seen in breast cancer, the translation of disease subtyping into a clinically-useful tool could take more than a decade.

Thus, we should probably consider a more comprehensive approach to identifying clinically-relevant HGSOC subtypes, taking into account not only the tumor expression profile but also tumor biology and the sequence of the events that might occur during tumor progression.

These considerations are somehow supported by the notion that HGSOC has a high degree of clonal heterogeneity at diagnosis, as demonstrated by massive parallel sequencing data. In fact, these analyses demonstrated that four or more different subclones could be identified within a single tumor mass in the vast majority of cases [2], and that a high degree of heterogeneity exists among different localisations of the neoplasm in the same patient [4, 5].

The "extra" value of gene expression signatures is based on the possibility that they can provide reproducible prognostic data, allowing scientists to identify potential new therapeutic targets and for physicians to specifically tailor treatment for an individual patient. However, by their very nature gene expression and/or sequencing studies often remain merely correlative and the translation of this vast genomic knowledge to the clinic is still not a trivial task.

Thus, on the one hand, gene expression profiles have certainly provided significant contributions to our understanding of the molecular profile of HGSOC and have unequivocally demonstrated that HGSOC comprises a complex mixture of different diseases. On the other hand, results obtained so far indicate that studies of gene expression profiling are not of immediate clinical utility. For instance, is not clear whether the different subtypes identified could benefit from different therapeutic approaches and/or should be included in ad hoc designed clinical trials.

This issue could be clarified, and maybe even solved, using two different strategies that require the collaboration of all stakeholders involved in HGSOC

Correspondence to:
Dr. Gustavo Baldassarre
Division of Experimental Oncology 2
Centro di Riferimento Oncologico,
Istituto Nazionale Tumori
Via Franco Gallini 2,
33081 Aviano (PN), Italy.
Phone: +39 0434 659759
E-mail: gbaldassarre@cro.it

research and care. The first strategy is a methodological approach based on the coupling of sequencing and gene expression data with functional studies. This approach could lead to the identification of more robust diagnostic tools and/or therapeutic targets. The second strategy is to combine the efforts of several translational research centers in order to compare, improve and standardise the type of treatments and collection of tissue samples, using pre-defined procedures. This will result in the collection of more homogeneous samples from homogenously treated patients. The design of prospective clinical trials, with clear translational endpoints, is probably mandatory across all oncology research, and for HGSOC in particular, and appears to be the only, or at least the most promising, way to accelerate the transfer of molecular knowledge to clinical practice.

Gustavo Baldassarre

Division of Experimental Oncology 2
Centro di Riferimento Oncologico, National Cancer Institute of Aviano, Italy

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