Commentary

A Combinatorial Investigation of the Response to Anti-angiogenic Therapy in Breast Cancer: New Strategies for Patient Selection and Opportunities for Reconsidering Anti-VEGF, Anti-PI3K and Checkpoint Inhibition

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More than 45 years ago, Judah Folkman (Folkman, 1971) postulated that proliferation, as well as the metastatic spread of cancer cells, depend on the formation of a new vascular network, and that by cutting off that blood supply a neoplastic lesion could be potentially starved into remission. Decades later, this hypothesis led to the blooming of a novel area of research, of an innovative approach to cancer treatment and, in turn, to the development and validation of clinically approved anti-angiogenic drugs such as the anti-VEGF monoclonal antibody bevacizumab (Kerbel, 2008). Anti-angiogenic therapies have been approved for the treatment of several types of cancer but the mechanisms of their anti-tumor activity remain incompletely understood (Jayson et al., 2016; Bertolini et al., 2010). Moreover, the limited clinical benefit reported in several trials has called the initial enthusiasm into question. In fact, in spite of potent anti-cancer activity reported in preclinical trials, a meaningful improvement in the overall survival of patients has been observed only in a few types of cancer, and almost all of the treated patients have experienced a clinical relapse (Kerbel, 2008; Jayson et al., 2016; Bertolini et al., 2010). Clinically-efficient anti-angiogenesis has turned out to be more complex than originally thought for many reasons: the multiple mechanisms employed by tumors to recruit blood vessels; the heterogeneity inherent in all cancer subtypes; the complexity of interactions between endothelial and pericyte vessel cells and other components of the microenvironment, and the lack of validated predictive/prognostic biomarkers that could help clinicians to identify patients who are more likely to derive benefit from the treatment. Most of the biomarkers studies have focused so far on a) circulating biomarkers, often unable to separate reactive responses of the host from those of neoplastic lesions; and b) tissue biomarkers, based generally on a single biopsy that do not account for the intrinsic heterogeneity of multiple metastatic neoplastic lesions. With the recent emergence of novel high-throughput technologies in the era of personalized therapy, the field of biomarker discovery continues to be the subject of intense research. Innovative approaches in genomics, proteomics and multi-parametric imaging have facilitated simultaneous analysis of clinical, pathological, and genetic profiles along with the assessment of response to the treatment.

Radiogenomics, a multidisciplinary approach aimed at creating a link between molecular diagnostics and diagnostic imaging (Rutman & Kuo, 2009), is becoming an interesting emerging area of research, with the potential to directly and significantly influence clinical practice. The radiogenomic approach could allow the identification of robust, non-invasive biomarkers based on patients’ genomic, cellular and microenvironment alterations. This is potentially of paramount clinical relevance to the design and implementation of clinical trials. Unfortunately, a very limited number of trials have used and applied this approach so far. Preliminary studies such as the one published here by Mehta and coworkers (Mehta et al., 2016), provide promising and potentially powerful new tools for the understanding of tumor biology in terms of response to anti-angiogenesis therapy and mechanisms of acquired resistance. This might lead to the validation of predictive/prognostic and dynamic biomarkers for clinical care. Authors took advantage of a well-designed window-of-opportunity trial where 35 ductal breast cancer patients received the anti-VEGF antibody bevacizumab alone, prior to neoadjuvant (i.e. before-surgery) chemotherapy. By means of correlative associations between Dynamic Contrast Enhanced-Magnetic Resonance (DCE-MRI) parameters and changes in histological markers and gene expression, Mehta et al. (Mehta et al., 2016) demonstrated that in responder patients, the response to bevacizumab was detectable even after a very short time of treatment and was much more complex and heterogeneous than anticipated, involving different pathways including angiogenesis (e.g. ESM1 and FLT1), proliferation and cell death genes and proteins. In...
non-responding patients authors observed the up-regulation of cancer-related glycolysis, hypoxia, PI3K-Akt and immune checkpoint inhibition signaling, suggesting a novel and potentially targetable adaptation mechanism of resistance.

Taken together, these features can be used as biomarkers for more precise and earlier prediction of the biological features and prognosis of breast cancers, so as to drive patient selection and enrollment in tailored clinical trials. Most of all, this new insight on the molecular and cellular mechanisms of resistance to the anti-VEGF treatment in breast cancer might stimulate new combinatorial and sequential therapies with anti-angiogenic, anti-PI3K and immune checkpoint inhibitors. Anti-PI3K drugs and checkpoint inhibitors (such as anti-CTLA4, anti-PD-1 and anti-PD-L1) are currently under clinical investigation in breast cancer and in other types of malignancies. Unfortunately, in most cases these new drugs are used alone and not in sequential and/or combinatorial strategies.

Preliminary data by Mehta et al. (Mehta et al., 2016) need to be further investigated for reproducibility and validated in larger cohorts of patients, but results are already based on three different models showing similar results. Because of the lack of validated predictive/prognostic and/or dynamic biomarkers, the clinical use of bevacizumab in breast cancer is nowadays much more limited (if used at all) than in the early years after clinical approval in the US, EU and Asia (Bartsch et al., 2015). These data suggest a possible re-evaluation of this drug based upon early classification of resistant/refractory patients. New innovative clinical trials might now be designed taking into account the dynamic monitoring suggested by Mehta et al. (Mehta et al., 2016) and a combination approach with anti-PI3K and checkpoint inhibitors. Hopefully, this approach might prolong the quality of life and the survival of the limited number of breast cancer patients who are actually sensitive to VEGF inhibition, while sparing other patients unnecessary, expensive and sometimes toxic treatments.

References

Bartsch, R., Gnant, M., Steger, G.G., Sep 2015. Bevacizumab: no comeback in early breast cancer? Lancet Oncol. 16 (9), 1001–1003.

Bertolini, F., Marighetti, P., Shaked, Y., 2010. Cellular and soluble markers of tumor angiogenesis: from patient selection to the identification of the most appropriate post-resistance therapy. Biochim. Biophys. Acta, Rev. Cancer 1806, 131–137.

Folkman, J., Nov 18 1971. Tumor angiogenesis: therapeutic implications. N. Engl. J. Med. 285 (21), 1182–1186.

Jayson, G.C., Kerbel, R., Ellis, L.M., Harris, A.L., Feb 4 2016. Antiangiogenic therapy in oncology: current status and future directions. Lancet pii: S0140-6736(15)01088-0.

Kerbel, R.S., May 8 2008. Tumor angiogenesis. N. Engl. J. Med. 358 (19), 2039–2049.

Mehta, S., Hughes, N., Li, S., Jubb, A., Adams, R., Lord, S., Koumakis, L., van Stiphout, R., Padhani, A., Makris, A., Bufla, F., Harris, A., 2016. Radiogenomics monitoring identifies metabolism and immune checkpoints as early actionable mechanisms of resistance to anti-angiogenic treatment. ElBioMed. 10, 109–116.

Rutman, A.M., Kuo, M.D., May 2009. Radiogenomics: creating a link between molecular diagnostics and diagnostic imaging. Eur. J. Radiol. 70 (2), 232–241.