Towards precision medicine: CCL2, another brick in the wall?

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Research for predictive biomarkers that are crucial to decisions for targeted treatments is very important; the data should be validated in large studies http://ow.ly/mzis30neEA6

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The introduction of targeted treatment in lung cancer has substantially changed the outcome of disease and the lives of lung cancer patients. Having biomarkers that can identify the right candidates and that predict the response to a specific treatment is very important and currently, research focuses on the identification of reliable molecular markers. In this issue of the *European Respiratory Journal*, Lu *et al.* [1] provide insight into the mechanisms of action of a new medication, anlotinib, and propose a new, predictive biomarker, the C-C motif ligand 2 (CCL2).

Anlotinib is a multi-target tyrosine kinase inhibitor; it acts on vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptors, fibroblast growth factor receptor and c-kit. A previous study from the same group, showed that anlotinib therapy was beneficial in prolonging overall survival in heavily pre-treated nonsmall cell lung cancer (NSCLC) patients [2]. In the current study by Lu *et al.* [1], the authors retrospectively screened for the presence of biomarkers of anlotinib response in a subgroup of patients from the original cohort. The study showed that anlotinib therapy was beneficial in prolonging overall survival in NSCLC patients harbouring positive driver gene mutations, especially patients harbouring the epidermal growth factor receptor (EGFR) T790M mutation. Moreover, the researchers found that benefits in progression-free and overall survival in refractory advanced NSCLC were associated with anlotinib-induced serum CCL2 level decreases. So, the study indicates that patients exhibiting specific mutations respond to targeted treatment, in line with the current treatment practice and, importantly, the authors report a novel anti-angiogenetic mechanism of anlotinib *via* inhibiting CCL2. They also suggest that changes in serum CCL2 levels may be used to monitor and predict clinical outcomes of anlotinib administration in refractory advanced NSCLC patients [1, 2].

Having predictive markers is pivotal when deciding on medications that can affect the patients' survival and that are expensive and potentially toxic. Over the past decade, our understanding about cancer as well as the treatment choices for its management have grown exponentially. Research into lung cancer in particular, has become a pioneer into precision medicine efforts. Since 2004, when the first specific activating mutations within the tyrosine kinase domain of the EGFR gene were identified and shown to correlate to a dramatic response to EGFR-TKI treatment, huge progress has been made [3]. Today, guidelines and recommendations suggest evaluation of EGFR, ALK, and ROS1 for all patients with metastatic nonsquamous lung cancer, irrespective of their clinical characteristics, and, targeted therapy is

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preferred over chemotherapy when these mutations are detected [4]. Not only EGFR, ALK and ROS1 status but also a broader panel of genes can be tested, including BRAF, RET, ERBB2 and MET, and this testing will be more accessible when next-generation sequencing is available. This is important as one or more targeted therapies are available for patients who exhibit these gene alterations. And, more recently, programmed death-ligand 1 (PD-L1) expression has been added as a molecular marker, since new treatments using anti-programmed cell death-1 antibodies have been approved as first-line monotherapy in the subpopulation of patients with a high tumour proportion score, and PD-L1 positivity in >50% of tumour cells [5].

Angiogenesis is a survival mechanism for tumours. With the deeper understanding of the role of angiogenesis in lung cancer progression and metastasis, drugs that have an inhibitory action on the vascular endothelium have been incorporated into lung cancer treatment. An example of such preparations is the anti-VEGF monoclonal antibody, bevacizumab [6]. Other anti-angiogenetic agents, such as ramucirumab [7] and nintedanib [8], are being tested as candidates to be added into the NSCLC treatment armamentarium. However, the initial enthusiasm regarding the potential of these drugs has faded rapidly both because of their modest increase in survival rates, but, mainly, due to the lack of predictive biomarkers. Although of great clinical importance, the implementation of molecular biomarkers that can predict the responses to inhibitors of angiogenesis in practice still remains something of a treasure hunt; such biomarkers are very difficult to characterise and validate. Previous randomised controlled trials have evaluated the importance of VEGF genetic variants and of soluble adhesion molecules, such as intercellular adhesion molecule (ICAM)-1, levels in plasma, through polymerase chain reaction assays, before and after chemotherapy/VEGF antibody combination administration [9–11]. Higher baseline soluble VEGFR and/or ICAM-1 levels were associated with poorer outcomes. However, it has not been proven that these molecules can be used as independent predictive biomarkers in lung cancer, and further evaluation is required [9–12]. The interesting aspect of the study by Lu *et al.* [1] is that they evaluated CCL2 as a marker for monitoring and predicting the clinical outcomes of anlotinib therapy. Moreover, as previously mentioned, the researchers used serum and not tissue and this could be an important asset. The increased need for molecular signatures makes the availability of tissue pivotal; nevertheless, it is often critical to avoid invasive techniques in patients who might have a relatively poor performance status. Unfortunately, the authors only managed to use samples from 14 of the 296 patients randomised on the anlotinib arm of the original study; thus the results, although interesting, cannot be considered conclusive. If these results are confirmed by larger trials, then an unmet goal of precision administration of anti-angiogenic factors could be fulfilled.

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