Afatinib, a lung cancer inhibitor of ErbB family

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In this issue, Modjtahedi and colleagues present the preclinical profile of “afatinib”, a new promising molecule, for the treatment of molecularly defined subgroups of patients with advanced lung cancer. Lung cancer is the leading cause of cancer-related mortality worldwide, and it results in more than 1 million deaths per year. The main types of lung cancer are small-cell lung carcinoma (SCLC), also called “oat cell cancer”, and non-small-cell lung carcinoma (NSCLC), occurring in about 85 % of lung cancer patients (Reck et al. 2013). Generally, at diagnosis, more than 80 % of NSCLC cases are in advanced stage (IIIB or IV) for which systemic chemotherapy remains the standard care but often provides only marginal improvement in survival (Sequist et al. 2013). In more than half of the patients with NSCLC, epidermal growth factor receptor (EGFR)-dependent pathway plays an important role driving the development and progression of epithelial cells (Yang et al. 2013). Afatinib [BIBW 2992;N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(dimethylamino)-2-butenamide] is an ATP-competitive anilinoquinazoline derivative harboring a reactive acrylamide group and belongs to a family of new small molecules which bind covalently the tyrosine kinase domain of ErbB receptors acting as tyrosine kinase inhibitors (TKIs) (Singh et al. 2011). Differently from the first generation of these molecules (erlotinib and gefitinib), afatinib, through its covalent bond, irreversibly blocks enzymatically active ErbB receptor family members (Solca et al. 2012).

The authors have outlined the mechanisms of ERB inhibition by afatinib, underlining the capability of this molecule to inhibit both the spontaneous EGF-induced autophosphorylation of EGFR and the EGFR stimulated by its ligands, in the low nanomolar range.

Furthermore, the drug potency was observed both in wild-type and EGFR mutations revealed in several cancer cell types, including L858R, which occurs in EGFR-mutant patients with a frequency of approximately 43 %, and in a “second-site mutation” T790M, which can be detected in 50 % and more lung cancers patients that have developed an acquired resistance to erlotinib or gefitinib.

Although preclinical experiments suggest the ability of afatinib to counteract tumorigenesis driven by T790M mutation, in clinical trials, there are doubts related to its full efficacy, showing minor expected improvements in patient response, similarly to the other EGFR inhibitors which can also cause resistance by prolonged exposure (Brugger and Thomas 2012; Gainor and Shaw 2013). In viewing cancer as an evolving process, it is reasonable to think that the ability to evade drugs, by neoplastic disease, might be associated with the development of new features. Thus, tailored drugs are able to eradicate cancer cells harboring the “targetable marker” but often produce resistance mechanisms causing only partial and temporary responses in patients. To this end, it would be of note to cite unambiguous studies, analyzing in details those targeted therapies and the crucial contribution of environmental factors to treatment responses and answering the question on how cancer is able to counteract those therapies (Yao et al. 2010; Sun et al. 2012; Weizman et al. 2013), thus definitively suggest the existence of a further layer in the complexity of cancer-drug resistance. Therefore, we might question whether these tailored drugs are the best choice for cancer therapy or whether the clinical use of molecular-targeted therapy treatment should be taking into the account the possibility of adjunctive therapies, based on the unique genetic-driven biology in each patient.

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To this end, the authors have analyzed the combinatorial use of afatinib with other inhibitors targeting both ErbB signaling pathway and/or specific downstream molecules of other signaling pathways, e.g., MEK, Akt, PI3K, mTOR, or STAT3, showing cases where afatinib alone had little effect on cell survival, while in the presence of another inhibitor, which did not affect survival on its own, became more potent. Prospectively, we should stay tuned for more details about these trials that would result in a benefit for patients. The data presented by Modjtahedi and colleagues refer that the greatest effort to the development of new anticancer therapies should be directed to the combinatorial use of existing drugs, rather than in searching new molecules, and also towards a more individualized view of molecular alteration that will likely influence stratification of patients by physicians. Further refinement of these studies on combinatory treatment will surely help the management of patients.

As a drug discovery effort, afatinib presents several issues of discussions, telling a true story which outlines the difficulties encountered from the new molecule's idea till its efficacy and use in clinical trial.

The long list of examples provided by the authors demonstrate that afatinib has ample opportunities for combinations with other targeted agents, foreseeing that this molecule might be eligible for future appropriate treatment regimens, that should lead to new routes of attaining durable responses.

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