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Gefitinib

A Viewpoint by Fortunato Ciardiello

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Gefitinib (ZD1839) is an orally active, epidermal growth factor receptor (EGFR)- selective tyrosine kinase inhibitor. The phase I/II clinical trial program has demonstrated a significant antitumor activity of gefitinib as single agent therapy in various epithelial cancer types. Particularly encouraging are the results from the two phase II IDEAL trials in patients with pretreated advanced non-small cell lung cancer (NSCLC) who had failed one or more conventional cytotoxic treatment regimens.

Gefitinib has shown an excellent tolerability profile in clinical trials with very mild and reversible adverse effects. This is clinically relevant since it could allow the use of gefitinib in combination with conventional cancer treatments without increasing their toxicity and since it could permit their use as long-term therapy in different clinical scenarios including the adjuvant setting, maintenance treatment in metastatic disease and possibly, chemoprevention.

Several clinically relevant questions on the use of EGFR-targeted therapies, such as gefitinib, are emerging. Firstly, is not clear how important it will be to select cancer patients for treatment with these drugs based on the levels of EGFR expression within the tumor. Although it is necessary that cancer cells express functional EGFRs, it could be equally relevant for an optimal clinical response to EGFR inhibitors to measure the levels of expression of the other three EGFR-related growth factor receptors and of the EGFR selective ligands such as transforming growth factor-α. Secondly, the integrity of the EGFR-activated, signal transduction machinery could influence the response to these drugs. Recent experimental evidence suggests that cancer cells may escape from growth inhibition by using alternative growth pathways or by constitutive activation of downstream signaling effectors. Thus, it is conceivable that multiple growth controlling pathways are altered in cancer cells and so the combination of biologic therapeutics targeting two or more such pathways should be tested in a clinical setting. This will allow a poly-targeted treatment that is based on a rational approach to the alterations that are present in a cancer patient. ▲