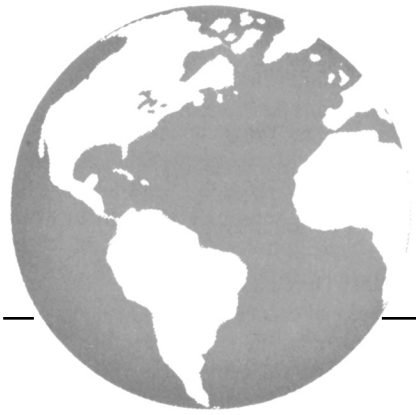
Curr Oncol, Vol. 19, pp. S86; doi: http://dx.doi.org/10.3747/co.19.1049

CONCLUSION



Future of personalized medicine in non-small-cell lung cancer

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The remarkable progress we are witnessing in the understanding of the molecular biology and signalling pathways of non-small-cell lung cancer (NSCLC) cells has resulted in ErbB-targeted therapies and many other targeted agents, especially Alk inhibitors, now in clinical trials. However, a substantial proportion of NSCLC patients remain nonresponsive to or relapse early on these therapies. Improved understanding of the functioning of the ErbB receptor family has led to additional second-generation active anti-ErbB therapies. Various preclinical and clinical studies have clarified that, when combined, anti-ErbB therapies have an efficacy superior to that seen with single-agent strategies. An understanding of the development of resistance to certain targeted agents is very important in efforts to prevent such resistance.

In future, it will be essential to characterize mutations of resistance in each line of treatment and to segregate patients accordingly. Co-targeting one or more molecular pathways such as PI3K–Akt, Ras–Erk, T790M, and c-Met, together with ErbB receptors, may produce anticancer effects that are more optimal.

We need to better understand the interplay between various oncogenes and tumour suppressors, thus identifying key molecular pathways for therapeutic interventions. Work on preclinical murine models to further an understanding of the reasons for toxicities and development of resistance will be important to support future rational treatment approaches for combining or sequencing various targeted agents. Co-targeting receptors and their ligand synthesis might help to completely eliminate receptor activation and downstream oncogenic signalling. Future investigations may provide new insights into autocrine activation of receptors and uncover new therapeutic approaches.

It will become extremely important to understand the key receptor regulators involved in receptor degradation or recycling. An ubiquitin lipase c-Cbl involved in internalization and degradation of the epidermal growth factor receptor (EGFR) is frequently mutated or lost in lung cancer [1]. Similarly, stress-activated kinases such as p38 have been implicated in EGFR recycling and endosomal accumulation. Those events may contribute to resistance to antibody or tyrosine kinase inhibitors in the treatment of NSCLC [2]. Thus, co-targeting key pathways involved in receptor recycling and receptor activity may increase treatment efficacy and decrease the development of tumour resistance.

The past successes and failures of therapies and the reasons behind them led to development of new-generation irreversible ErbB family inhibitors and the discovery of new targets such as the *EML4–ALK* fusion gene, which offer significant improvement in clinical outcome for specific groups of patients. The combined-regimen strategies of first-generation ErbB family inhibitors with anti c-Met inhibitors are being tested in ongoing clinical trials in the hopes of improving therapeutic effect. Multiple pivotal players supporting malignant cells have to be targeted on an individual basis, in each line of treatment, to be able to replace "chemotherapy to fit all" with personalized medicine and the potential to thereby conquer NSCLC. The ability to analyze circulating tumour cells or plasma DNA for various targets on an individualized basis should eventually help to more conveniently find an appropriate therapy for each patient.

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