Mutation explains relapse on EGFR products

A discovery made simultaneously by two groups of US researchers may help lung cancer patients who relapse after an initial response to novel targeted therapies.

Scientists have discovered an epithelial growth factor receptor (EGFR) mutation that could explain why non-small-cell lung cancer (NSCLC) patients relapse on the EGFR tyrosine kinase inhibitors Iressa and Tarceva, after an initially good response.

Two teams seem to have raced each other to press with the publication of two papers coming just two days apart.

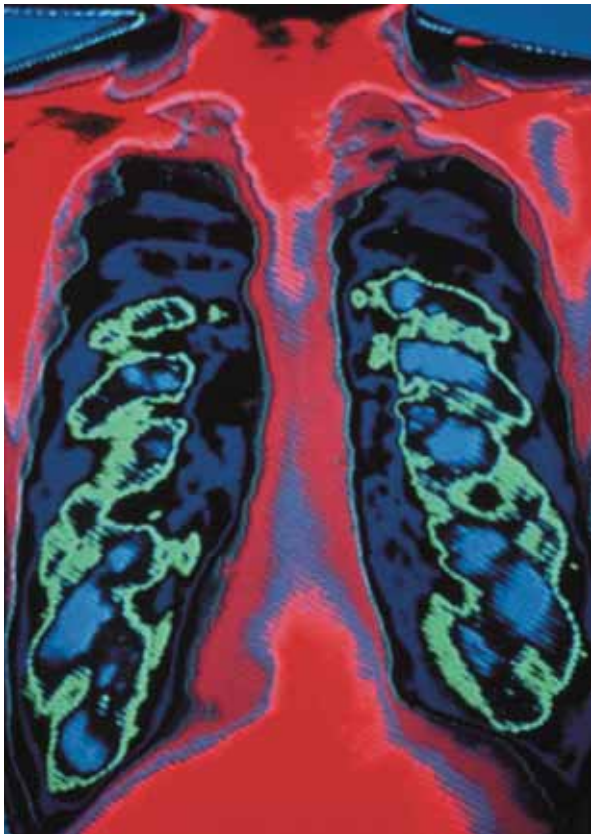
The research could be important for the development of second-generation EGFR inhibitors and could help refine the use of Roche/OSI/Genentech's Tarceva (erlotinib) and AstraZeneca's Iressa (gefitinib), although the latter is facing an uncertain future after it failed to show a survival benefit in the phase III ISEL (Iressa Survival Evaluation in Lung Cancer) study.

A group of researchers from the Memorial Sloan-Kettering Cancer Center had their work published online on February 22nd in *PLoS Medicine*[1], ahead of its print version in March.

The other team, which was led by Balazs Halmos from the University Hospitals of Cleveland, published its research as a brief report in the *New England Journal of Medicine* (February 24th, p786). The results add to findings last year that patients who responded to Iressa therapy had mutations in EGFR that sensitised them to the drug.

The Memorial Sloan-Kettering team discovered the new mutation, T790M, in three out of six patients resistant to either Iressa or Tarceva and confirmed the finding in an NSCLC cell line. The other scientists found T790M in a 71-year-old man who had 24 months of complete remission on Iressa before relapsing.

It is not yet clear how the mutation arose. However, after surveying 150 tumours and reviewing the literature, the Memorial Sloan-Kettering researchers think it is probably extremely rare in NSCLC tumours that have not been treated with either drug. The mutations could either arise de novo during treatment, or else subclones with the mutation could become



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[1] *PLoS Medicine* is published by the Public Library of Science – a non-profit organisation of scientists and physicians committed to making the world's scientific and medical literature a freely available public resource.

T790M corresponds structurally to a mutation that commonly causes resistance to imatinib in CML

more prevalent as Iressa/Tarceva-sensitive cells die.

The mutation does not appear to be the only reason for resistance to Iressa or Tarceva. The Memorial Sloan-Kettering researchers found that a further three resistant patients did not have the T790M mutation. They also note that T790M is distinct from the KRAS gene, which is known to cause primary resistance to the products, and EGFR over-expression could also be a source of resistance. The authors of the NEJM paper suggest that the development of a new EGFR mutation shows that the tumour cells remain dependent on EGFR for their proliferation.

Second generation

Understanding exactly how T790M stops cells responding to Iressa or Tarceva could help design second-generation inhibitors. It seems, from crystal structure analyses, which both teams carried out, that an amino acid substitution caused by T790M creates a steric clash so the products cannot bind to EGFR, but the mutation does not stop the receptor from functioning. Therefore, products that bind to EGFR in a different way would be less affected by T790M.

After looking at structural data on the compound, the Memorial Sloan-Kettering team speculates that GlaxoSmithKline's dual EGFR/Her2-targeting anticancer, lapatinib, could have a role in resistant patients, although they note it has not yet been tested in this population. Lapatinib is in phase III trials for lung cancer, although the lead indication is breast cancer.

In a *PLoS Medicine* Perspective piece published with the paper, Gary Gilliland from Harvard Medical School and colleagues say there should be a more proactive approach to developing drugs to tackle resistance. "In vitro screens for mutations that confer resistance to kinase inhibitors are warranted, followed by effort to identify drugs that overcome resistance."

Imatinib parallels

The discovery of the new mutation mirrors the experience with Novartis's Bcr-Abl tyrosine kinase inhibitor, Glivec (imatinib), the authors of both papers note. Knowledge of the mechanisms of resistance – point mutations or amplification of the BCR-ABL gene – has helped develop second-generation products such as Bristol-Myers Squibb's BMS-354825 and Novartis's AMN107. These products bind to ABL in an 'open' rather than 'closed' conformation, leaving them less susceptible to mutations to the binding site. Another parallel with understanding on imatinib could help predict drug resistance in similar products in future. This is because T790M corresponds structurally to a mutation which commonly causes resistance to imatinib in chronic myelogenous leukaemia. "This finding suggests that there are mechanisms of drug resistance common to tyrosine kinase inhibitors that could be predicted from the start," say Jonathan Dowell and John Minna from the University of Texas Southwestern Medical Center in an accompanying editorial in the NEJM (p 830).

The authors of the NEJM study think the research "underscores the need to consider incorporating repeated biopsies into clinical studies of novel targeted therapies." Gilliland and colleagues agree that patients who relapse should have a re-biopsy. "It is clear that data derived from such analyses will be essential to inform approaches to improving therapy for NSCLC and other solid tumours."

Dowell and Minna also note "It will be important to discover at what stage in the pathogenesis of lung cancer EGFR mutations occur." If they are found in preneoplastic lesions, they suggest that patients could be given relatively non-toxic tyrosine kinase inhibitors to avoid the use of chemotherapy.

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