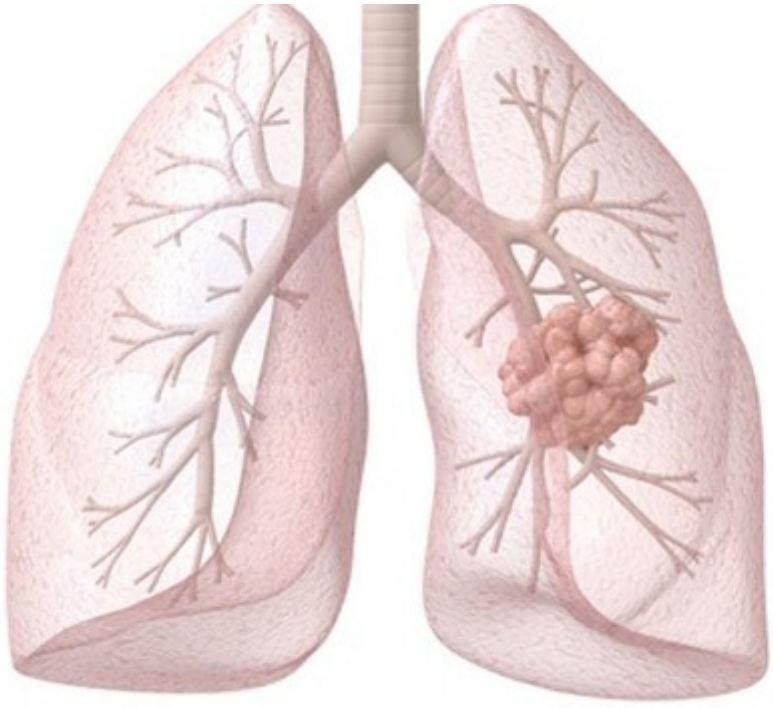
Healthcare industry BW

Biomarkers to combat lung cancer

A biomarker-driven personalised therapeutic approach to lung cancer is possible – this is the conclusion reached by the BATTLE trial. The preliminary results of the trial were summarised by scientists from the Thoraxklinik at Heidelberg University Hospital in the May 2011 issue of "Clinical Investigation".



Lung cancer, schematic

In Europe and North America, a far greater number of people die from lung cancer than any other cancer. The American National Cancer Institute estimates that there were around 160,000 deaths from lung cancer in 2009 and around 220,000 newly diagnosed cases. The ratio between deaths and newly diagnosed lung cancers was even worse in Germany where there were 40,000 deaths and 46,000 newly diagnosed cases. The number of lung cancer cases and deaths is also on the increase in many other countries. Lung cancer is a particularly malignant cancer as it is often only diagnosed when it has already spread throughout the lungs or to other organs to the point where it cannot be surgically cured. Treatment of lung cancer with chemotherapy generally also has a poor diagnosis.

Growth factors as new drug targets

Great expectations for the more effective treatment of lung cancer are being placed on a new generation of drugs that target the regulatory mechanisms of cell growth, in particular cancer cell growth mechanisms. The most promising drugs include protein kinase inhibitors which act as growth factor receptor antagonists, in particular for EGFR (epithelial growth factor receptor), VEGFR (vascular endothelial growth factor receptor) and PDGFR (platelet-derived growth factor receptor).

Prof. Dr. med. Michael Thomas, Head of the Department of Internal Medicine, Thoracic Oncology, Thoraxklinik/University of Heidelberg

The researchers found that the drugs tested had different effects in different lung cancer patients, ranging from excellent to no effect at all. Professor Dr. Edward Kim from the M. D. Anderson Cancer Center at the University of Texas, USA, explains: "New drugs that target molecular signalling pathways help a small percentage of lung cancer patients, but right now there's no way to determine who those patients are before treatment." A large clinical trial known as BATTLE was initiated at the M. D. Anderson Cancer Center in 2005 with Dr. Kim as principal investigator. The preliminary results of the trial, which is aimed at finding biomarkers for making predictions about the effect of particular drugs, have now become available.

PD Dr. med. Niels Reinmuth, senior consultant in the Department of Internal Medicine, and Professor Dr. med. Michael Thomas, head of the Department of Internal Medicine (Thoracic Oncology) at the Thoraxklinik at Heidelberg University Hospital, were both involved in BATTLE and have summarised the results in the journal "Clinical Investigation". The Thoraxklinik, a not-for-profit limited liability company (GmbH), is part of Heidelberg University Hospital and is one of the oldest and largest lung specialist clinics in Europe.

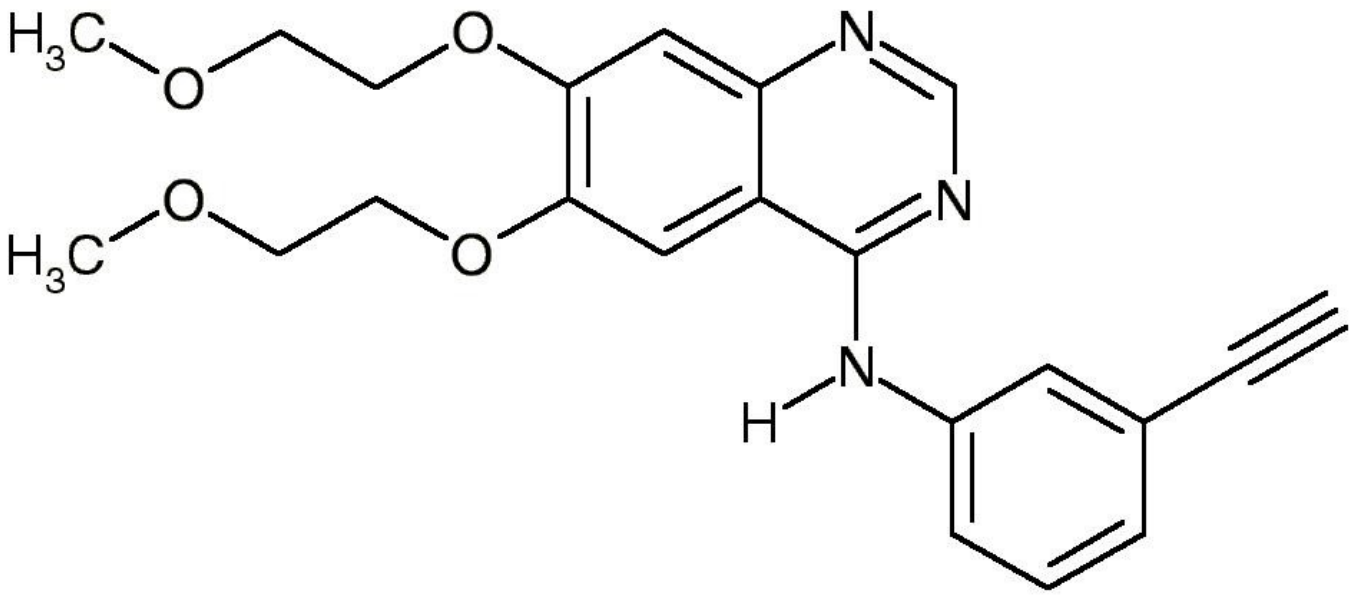
War against cancer

The rather militant term BATTLE was chosen deliberately for a number of reasons: it alludes to the ongoing battle being waged by medical science against this malignant disease; the former US President George W. Bush once called for a "war against cancer". The term is also intended to make people think of lung cancer patients' struggle for survival. In addition, the name refers to the major sponsor of the trial – the "United States Army Medical Research Program". However, all these reasons aside, BATTLE is actually an acronym for "Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination".

BATTLE is a Phase II clinical trial in which four drugs were matched to specific molecular signatures

(biomarkers) and their effect on patients being treated for lung cancer (stage IV non-small cell lung cancer) was evaluated. “We evaluated tumour biomarkers in the hope of treating lung cancer like we treat breast or colon cancer using validated biomarkers to guide treatment and improve survival time,” said Kim explaining the objectives of the trial. “Previous lung cancer research has been plagued by large Phase III clinical trials that showed minor effects or even failed to enrol enough patients to finish,” Kim said.

Mutations as biomarkers



Erlotinib (Tarceva®), structural formula
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Even though two lung cancer tumours might appear identical under a microscope and have the same staging, they can still behave differently. It is therefore crucial to treat each lung cancer patient based on the unequivocal molecular defects in the tumour. The drugs tested included new low molecular substances that are designed to block specific cellular signalling pathways that are important for tumour growth, including erlotinib (marketed by Roche as Tarceva®), sorafenib (Nexavar®; Bayer), vandetanib (Zactima®, marketed as Caprelsa® since August 2011; AstraZeneca) and bexarotene (Targretin®; Elsal), which was administered together with bexarotene. Erlotinib, sorafenib and vandetanib are protein kinase inhibitors that target signalling chain receptors. Bexarotene is a retinoid that prevents the dimerisation of the retinoid X receptors and hence makes it impossible for them to bind to DNA.

At the beginning of the BATTLE trial, the participants were statistically distributed to the four drug groups. All patients agreed to have a new biopsy for the trial, which was crucial for the study design as it provided fresh information on the tumour's molecular status that may have been altered by treatment since the patient's previous biopsy. In their paper in "Clinical Investigation", Reinmuth and Thomas highlighted the increasing importance of re-biopsies of metastatic diseases as one of the significant results of the BATTLE trial. "Biopsies should be performed in conditions of acceptable risk for the patient, and should be combined with other treatment options whenever possible," said the two scientists from the Thoraxklinik in Heidelberg.

Strategy for more effective treatment

As the trial progressed, the information obtained from patients' biopsies and their reactions to the drugs were used to guide the assignment of drugs to new patients. These patients became more likely to be given a drug that had worked for previous patients with the same tumour biomarkers. In addition, the strategy led to the reduced use or dropping of drugs that were less successful. The study found that vandetanib gave the best results in patients whose lung cancer was characterised by VEGFR overexpression; the drug was not used in patients with a KRAS mutation in their tumours. In such cases, sorafenib proved to be the best drug. Patients with EGFR mutations responded best to erlotinib treatment and patients with cyclin D1 gene defects or amplified numbers of the EGFR gene responded best to bexarotene/erlotinib treatment.

Thoraxklinik in Heidelberg-Rohrbach

The data open up interesting areas for future research. The identification of genetic markers in metastasising non-small-cell lung cancer - and hence the ability to guide the use of specific drugs for specific lung cancer patient populations - also permits another important conclusion to be drawn: Phase III clinical trials, i.e. randomised multicentre trials on large patient groups (up to several thousand patients, depending on the medical condition studied) aimed at coming up with a definitive assessment of the effectiveness of the drug under investigation, can henceforth be carried out with a smaller number of patients and will therefore take less time.

BATTLE thus opens up the promising perspective that lung cancer can also be treated using a personalised therapeutic approach involving drugs based on molecular signatures (biomarkers) in tumour biopsies. It can be safely assumed that BATTLE has not yet won the decisive battle in the "war against cancer", but it has shown the way towards eventual victory in the battle against lung cancer.

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Article

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The article is part of the following dossiers

Development of new molecular biomarkers