Targeted Therapy in Lung Cancer

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Lung cancer is one of the most common cancer types world-wide and a main cause for cancer-related death in both, men and women with (with overall 5 years survival rate of less than 20%). Histologically more than 80% of lung cancers are non-small cell lung carcinomas (NSCLC), including adenocarcinomas, squamous cell carcinomas, and large cell carcinomas. Less than 20% refer to small cell lung carcinomas. In early stages of disease the treatment has curative intent (surgery, radio-/chemotherapy) but many patients suffer relapse of disease. In advanced tumor stages palliative chemotherapy is applied (mainly carbo- and cisplatin-based combinations) ¹. Based on the expanding knowledge in molecular tumour biology, components of the oncogenic pathways that regulate tumor cell growth, proliferation, and angiogenesis have been identified for targeted lung cancer therapy. The most common molecular genetic changes that are identified in NSCLCs are KRAS mutations (22%), EGFR mutations (17%), and ALK rearrangements (7%) ². Activating mutations in the EGFR-gene (exons 18-21) can confer sensitivity to EGFR tyrosine kinase inhibitors in patients with advanced NSCLC. Two types of mutations (in-frame deletions in exon 19 and the specific exon 21 point mutation L858R) are comprising up to 90% of all activating EGFR mutations. Gefitinib and erlotinib are orally administered small molecule EGFR tyrosine kinase inhibitors.

By Zhang and colleagues³ it was shown in a phase III trial (INFORM study) that treatment with gefitinib significantly prolonged progression-free survival in patients after first-line chemotherapy. In the IPASS study (a phase III trial) Mok et al.⁴ also demonstrated that gefitinib was superior over standard chemotherapy. One the contrary the study groups of Thatcher and Kim⁵,⁶ could not show any benefit from gefitinib therapy. But a recent meta-analysis by Wang et al.⁷ stated that first-line treatment with gefitinib conferred prolonged progression-free survival compared with systemic chemotherapy treatment in patients with NSCLC that harboured activating EGFR-mutations. Therefore the testing for these mutations is an important step in clinical trials evaluating the role of EGFR tyrosine kinase inhibitors.

More importantly, Rosell et al.⁸ and Zhou et al.⁹ investigated in two randomized trials (OPTIMAL and EURTAC OPTIMAL study) erlotinib monotherapy versus chemotherapy as first-line treatment in patients with advanced NSCLC and EGFR-mutation in Caucasian and Asian patients, respectively. In both studies a significant progression-free survival benefit over standard chemotherapy with 63% and 84% reduction in risk of progression was found (HR 0.37 and HR 0.16). A significant quality of life benefit with erlotinib over first-line chemotherapy was also stated.

The study group of Gridelli ¹⁰ had to stop a phase III trial because the first-line erlotinib followed by standard chemotherapy in case of tumour progression was significantly worse compared with the standard sequence of first-line chemotherapy followed by erlotinib in terms of overall survival. Lung tumor patients with EGFR-mutations benefit more likely of a tyrosin kinase inhibitor therapy ¹¹ but EGFR-mutation-negative patients (wild type) might also respond to such a therapy¹².

The epidermal growth factor receptor (EGFR) is frequently overexpressed in NSCLCs. Once activated it initiates a signal transduction cascade that promotes tumor-cell proliferation. Cetuximab is a monoclonal antibody that binds EGFR. It is well established as a therapy in colorectal cancer as well as squamous cell cancer of the head and neck. In the studies of Pirker et al. ¹³ and Ibrahim et al. ¹⁴ a prolonged progression-free and overall survival of locally advanced and metastatic NSCLC was obtained by a combination of platin-based chemotherapy and cetuximab. KRAS mutations in NSCLCs are associated with a poor prognosis. On contrary to coloncarcinoma an association between KRAS mutational status and lacking benefit of anti-EGFR monoclonal antibodies has not been found. As

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KRAS mutations are very common in NSCLCs they also might be a target for new therapeutic strategies in the KRAS downstream effector pathway.

Some NSCLCs harbour an EML4-ALK fusion protein mutation, especially in young, male, and never-smokers with adenocarcinoma subtype. It is associated with the lack of EGFR or KRAS mutations. In 2011 the USA approved crizotinib for treatment of late-stage NSCLCs with abnormal ALK gene, based on two phase II studies that had 50% and 61% overall response rate. In March 2013, the selective inhibitor of ALK, LDK378, showed a response rate of 80% in the patients who had experienced disease progression after crizotinib treatment. More clinical trials are initiated for further evaluation.

Human epidermal growth factor receptor 2 (HER2) is overexpressed in up to 20% of NSCLCs, mainly in the adenocarcinoma subtype, in women and never-smokers. Although the study of trastuzumab in HER2-overexpressing NSCLC did not identify significant clinical activity, the role of some of the aforementioned irreversible tyrosine kinase inhibitors targeting both EGFR and HER2 (afatinib and dacomitinib) has received recent attention in a phase II trial. BRAF is a serine/threonine kinase downstream from KRAS. Oncogenic BRAF mutations are rarely found in NSCLC (up to 5%). Approximately half of the mutations identified were V600E, and further studies are needed to find out whether these tumours are sensitive to V600E-specific inhibitors treatment. In small cell lung cancer a number of molecular targets have been identified in various preclinical studies, but no targeted agents have been approved for use in the treatment of SCLC patients to date.

In conclusion, there are some very promising new therapeutic agents in targeted therapy of advanced NSCLCs; more studies are required to learn more about novel agents, their effectiveness and improved patient selection based on clinical and molecular factors.

References


