Research Highlight

# EGFR-TKIs in EGFR-mutated lung cancer: setting the new standard for 1st line therapy

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Treatment of patients with advanced non-small cell lung cancer (NSCLC) harbouring activating mutations in the epidermal growth factor receptor (EGFR) with EGFR-directed tyrosine kinase inhibitors (TKI) has become a paradigm for the therapeutic potential of personalized cancer treatment. Never before treatment results were reported for a defined NSCLC subgroup comparable with the outcome reported in clinical trials evaluating treatment of EGFR-mutated NSCLC with either gefitinib or erlotinib. For instance, in a recent trial of the Spanish Lung Cancer Group 217 patients with EGFR mutated advanced NSCLC were treated with erlotinib either first- or second line with a remission rate of 71%, a median time to progression (TTP) of 14 months and a median overall survival time (OS) of 27 months (1).

Nevertheless, from a formal point of view, selection of a prognostically favorable subgroup characterized by the presence of activating EGFR-mutations can only be ruled out as an explanation for these results in randomized clinical trials comparing chemotherapy and EGFR-TKI treatment. By now, several such trials comparing gefitinib and platinum-based chemotherapy as first line treatment of EGFR-mutated Asian patients have been conducted (2-4). These trials consistently showed impressive superiority of gefitinib *vs*. chemotherapy with regard to remission rates and progression-free survival (PFS). In addition, the toxicity profile was significantly more favorable in the gefitinib treated patients. However, in none of these trials an improvement of the overall survival time could be shown. The underlying reason for this was the treatment of patients in the chemotherapy arms with gefitinib after relapse of the disease (crossover).

With the OPTIMAL study, published recently by Zhou and colleagues (5), for the first time erlotinib (83 pts.) was compared with chemotherapy (gemcitabine plus carboplatin, 82 pts.) in a randomized trial in previously untreated EGFR mutated NSCLC patients. The results are quite comparable to those reported previously for gefitinib. Median PFS was significantly longer in the erlotinib arm compared to the chemotherapy arm (13.1 *vs*. 4.6 months, HR 0.16). In addition, grade 3 and 4 toxicity was significantly increased in the chemotherapy arm. Again, due to the crossover effect, a survival benefit could not be demonstrated.

In view of the comparable biological mechanisms underlying gefitinib and erlotinib efficacy in EGFR-mutated patients, i.e., the enhanced affinity of the mutated kinase to ATP-competitive kinase inhibitors of the quinazoline type, the results of the OPTIMAL study could have been expected. Similiarly, in a recent randomized trial comparing erlotinib first line monotherapy with platinum-based chemotherapy in EGFR-mutated European patients (EURTAC), superiority of the erlotinib arm *vs*. the chemotherapy arm was reported in terms of response rates and PFS (9.7 *vs*. 5.2 months, HR 0.37), but not for overall survival (6).

Taken these data together, there is overwhelming evidence now that the currently approved EGFR-TKIs are superior to chemotherapy in EGFR-mutated NSCLC. But do we also have any evidence that one of these both drugs is superior to the other? A comparison of the PFS data reported in the Asian gefitinib trials (IPASS: 9.5 months, NEJ002: 10.4 months, WJTOG: 9.2 months) with those reported for erlotinib by Zhou (13.1 months) and the Spanish Lung Cancer Group (14 months) seems to implicate a superiority of erlotinib. Differences in the area under the curve (AUC) for erlotinib and gefitinib have been suggested as explanation. However, it should be emphasized that cross trial comparisons are of limited informative value based on substantial differences in the trial cohorts also in large randomized trials. The disappointing

PFS reported for erlotinib in the EURTAC trial (9.7 months) is in line with these considerations. Thus, without a head-to head comparison the superiority of one EGFR-TKI to another will remain an open question.

There is still an ongoing discussion among clinicians whether EGFR-TKIs should be used as first line treatment in EGFR-mutated NSCLC, since no survival benefit could be demonstrated in the randomized trials comparing these drugs with chemotherapy. Moreover, in the trial published by the Spanish Lung Cancer Group, overall survival was nearly identical, regardless whether patients received erlotinib first- or second line. Without doubt, prolongation of survival is (and should remain) one of the most prominent goals of any new cancer therapy. Hence, overall survival time is traditionally the key endpoint in clinical trials in oncology. However, we are learning now, that, in some contrast to the era of chemotherapy, more effective personalized treatment approaches result in substantially better response rates and PFS compared to standard therapy. In view of such pronounced differences with e.g., hazard ratios even below 0.2 for the PFS difference between erlotinib and chemotherapy in the OPTIMAL trial, it can hardly be justified to deprive a patient of the more effective drug, at least in the relapse situation. Thus, we have to recognize, that in the future for effective cancer drugs increasingly survival data will no longer be available from randomized trials. Instead, alternative endpoints, which should not necessarily be declared as surrogate endpoints, will gain in importance. In this context, PFS and RR are not only parameters allowing the assessment of the tumor-specific efficacy of a drug, but are also relevant from the patient's perspective. The latter applies particularly for toxicity. Results of the OPTIMAL trial confirmed, that EGFR-TKI treatment is by far less toxic with fewer SAEs compared to chemotherapy. Since there is no reason to start first line therapy with a less effective and more toxic drug, EGFR-TKI treatment should be defined as standard first line treatment of EGFR-mutated NSCLC.

For implementation of this personalized and effective treatment approach in clinical routine a high-quality and fast "real-time" genetic diagnostics is essential. Optimization of sample shipment logistics as well as benchmark analyses of currently available molecular test assays have to be performed. Also, invasive diagnostics has to ensure that enough tissue is available for molecular analyses and rebiopsies should be routinely performed in case of relapse to analyze molecular mechanisms of resistance.

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