Optimal front line treatment for European patients harboring *EGFR* mutations: Do longitude and race make a difference?

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For decades oncologists have been convinced that advanced non-small-cell-lung cancer (NSCLC) was a unique disease with an invariable rapid progression and with platinum based chemotherapy as the only available option for metastatic patients with acceptable performance status. During the past few years, the better knowledge of molecular mechanisms underlying this lethal disease moved researchers to leave this nihilistic attitude in favor of a positive perspective. This is the case of the Epidermal Growth Factor Receptor (*EGFR*) and its activating mutations, also named “*EGFR* wild type”- and on the other hand those harboring *EGFR* mutations. For the first group, standard platinum based chemotherapy, with pemetrexed and bevacizumab for adenocarcinoma and a combination of cisplatin and gemcitabine or taxanes or vinorelbine for squamous cell carcinoma, continues to be the gold standard of treatment.

From a practical point of view, in our daily clinical practice, we can dichotomise metastatic NSCLC patients in two groups according to *EGFR* status: on one hand those without *EGFR* mutations - also named “*EGFR* wild type”- and on the other hand those harboring *EGFR* mutations. For the first group, the study failed to demonstrated a survival advantage for gefitinib in unselected population (22.3 versus 22.9 months; HR 0.932, 95% CI 0.716-1.213; P=0.0640), although patients with *EGFR* mutations in the chemotherapy arm had lower PFS that those receiving gefitinib. The Iressa Pan-Asia Study (IPASS) randomized 1,217 patients with adenocarcinoma and unknown *EGFR* status to receive front line gefitinib or four cycles of carboplatin-paclitaxel (2). In the subgroup analysis of the 261 patients with proven *EGFR* mutations, a statistically significant improvement in PFS emerged for patients receiving gefitinib (PFS 9.5 versus 6.3 months; HR 0.48, 95% CI 0.36-0.64; P<0.001). Conversely, gefinitib treatment was detrimental in *EGFR* wild type patients (HR for progression or death 2.85; 95% CI 2.05-3.98; P<0.001). The WJTOG 3405 trial randomly assigned only *EGFR* mutant patients to gefitinib monotherapy or to four cycles of cisplatin-docetaxel (6). Subjects receiving gefitinib had longer PFS than did those in chemotherapy arm (9.2 versus 6.3 months; HR 0.49, 95% CI 0.34-0.71; P<0.001). In the NEJ002 trial, in which patients with *EGFR* mutations were randomly allocated to first line gefitinib or to four cycles of standard carboplatin-paclitaxel, treatment with gefitinib doubled PFS (10.8 versus 5.4 months; HR 0.30, 95% CI 0.22-0.41; P<0.001) (7). More recently, Zhou and colleagues published the results of the OPTIMAL trial, a phase III study comparing erlotinib monotherapy with carboplatin-gemcitabine in Chinese *EGFR* mutant patients (8). An impressive HR of 0.16 (95% CI 0.10-0.26) for PFS was reported for subjects allocated to experimental arm (median 13.1 months for erlotinib versus...

Vice versa, if we consider *EGFR* mutant patients, the best treatment option as front line therapy is *EGFR* TKIs, while platinum based chemotherapy could be a valid option as salvage therapy at the time of progression of disease. Five large randomized phase III clinical trials, conducted in more than 1,100 Asian patients with *EGFR* mutant NSCLC, have demonstrated that the best front-line therapy for these subjects is a tyrosine kinase inhibitor (TKI), such as Gefitinib or Erlotinib (2,5-10). The FIRST SIGNAL was a trial enrolling 313 Korean NSCLC patients with the primary end point of superiority of first-line gefitinib versus standard platinum-doublet chemotherapy in never smokers and adenocarcinomas (5). The study failed to demonstrated a survival advantage for gefitinib in unselected population (22.3 versus 22.9 months; HR 0.932, 95% CI 0.716-1.213; P=0.0640), although patients with *EGFR* mutations in the chemotherapy arm had lower PFS that those receiving gefitinib. The Iressa Pan-Asia Study (IPASS) randomized 1,217 patients with adenocarcinoma and unknown *EGFR* status to receive front line gefitinib or four cycles of carboplatin-paclitaxel (2). In the subgroup analysis of the 261 patients with proven *EGFR* mutations, a statistically significant improvement in PFS emerged for patients receiving gefitinib (PFS 9.5 versus 6.3 months; HR 0.48, 95% CI 0.36-0.64; P<0.001). Conversely, gefinitib treatment was detrimental in *EGFR* wild type patients (HR for progression or death 2.85; 95% CI 2.05-3.98; P<0.001). The WJTOG 3405 trial randomly assigned only *EGFR* mutant patients to gefitinib monotherapy or to four cycles of cisplatin-docetaxel (6). Subjects receiving gefitinib had longer PFS than did those in chemotherapy arm (9.2 versus 6.3 months; HR 0.49, 95% CI 0.34-0.71; P<0.001). In the NEJ002 trial, in which patients with *EGFR* mutations were randomly allocated to first line gefitinib or to four cycles of standard carboplatin-paclitaxel, treatment with gefitinib doubled PFS (10.8 versus 5.4 months; HR 0.30, 95% CI 0.22-0.41; P<0.001) (7). More recently, Zhou and colleagues published the results of the OPTIMAL trial, a phase III study comparing erlotinib monotherapy with carboplatin-gemcitabine in Chinese *EGFR* mutant patients (8). An impressive HR of 0.16 (95% CI 0.10-0.26) for PFS was reported for subjects allocated to experimental arm (median 13.1 months for erlotinib versus...
4.6 months for standard chemotherapy). Nevertheless, the huge difference in outcome between EGFR-TKI therapy and chemotherapy was related to unexpected low performance of the chemotherapy arm. Moreover, the chemotherapy regimen chosen as standard arm, the absence of an independent tumor response revision and, last but not least, the fact that investigators were informed that patients were all EGFR mutated could impacted on study results.

A topic question is if it is possible to translate these findings to European population. In fact we know that some differences exist between Asian and European patients: incidence of EGFR mutations is lower at our longitude and sensitivity to both chemotherapy and anti-EGFR TKIs seems not to be the same. This might simply reflect a different tumor biology or a different genetic make-up of the host.

In 2009, Rosell and colleagues published the results of a prospective trial designed with the aim to evaluate the feasibility of a large-scale screening for EGFR mutations in Spanish patients with metastatic NSCLC (9). According to trial design patients with proven activating EGFR mutations were considered for erlotinib, as first or subsequent line of treatment. Overall, 2,105 patients with advanced NSCLC from 129 centers were prospectively tested. Mutations were detected in 350 subjects (16%), mostly women, never smokers and with adenocarcinomas; of them, 217 received erlotinib treatment as first- (113 patients) or second-third line therapy (104 patients). Median PFS was 14 months, quite similar to than previously reported in Asian population. Two other important issues derived from this work: first, EGFR screening was feasible with laboratory results available in a reasonable time of seven days; second, testing EGFR mutations before starting therapy guided treatment choice.

In a recent issue of Lancet Oncology, the same authors (10) reported the final results of EURTAC trial, the first phase III study comparing erlotinib versus standard platinum-based chemotherapy as first line treatment in European patients with NSCLC harboring EGFR mutations. The study, enrolling 173 patients, met its primary end point of PFS. Patients treated with erlotinib had a 63% relative reduction in risk of progression compared with those receiving standard chemotherapy (9.7 versus 5.2 months, HR 0.37). Treatment with erlotinib was also associated with higher response rate (58% versus 15%, ITT population) and better toxicity profile. Notably, the subset analyses confirmed a significant PFS benefit in favor of erlotinib arm independently of age (>65 versus <65 years), gender, performance status (EGOG PS 0 versus 1 versus 2) and histology (adenocarcinoma versus other histologies). Subgroup analyses according to smoking status showed that the impact of the treatment was minimal in former smokers compared to current or never smokers in terms of PFS. This finding was unexpected and not in agreement with previous studies. In the OPTIMAL trial, as well as in WJTOG3405 and NEJ002 studies, both current and former smokers - even if evaluated as a single subgroup - had longer PFS when treated with TKIs. Similarly in the IPASS trial, in which eligible patients had to be never or light former smokers, no difference in PFS was seen between the two groups. It is not possible to exclude that the higher PFS benefit observed in the EURTAC trial in smokers versus former smokers was obtained by chance because of the very small number of patients included in these two subgroups.

Finally, it is important to highlight that in none of the above mentioned trials, the improvement in PFS translated in a significant advantage in overall survival in favor of gefitinib or erlotinib therapy for patients harboring EGFR mutations. In such trials in fact, the vast majority of patients assigned to the chemotherapy arm received an EGFR-TKI as second or third-line therapy, with an inevitable confounding effect on survival results. Despite this, in all trials a “clinically significant” trend in the hazard ratio for overall survival was slightly in favor of EGFR TKIs, reinforcing the conviction that if we consider EGFR mutant patients, they gain the greater benefit when an EGFR TKIs is administered early during the course of their disease.

In conclusion, all available data strongly support the usefulness of testing EGFR status in all patients with newly diagnosis of NSCLC in order to guide treatment selection and, finally, improve outcomes. In presence of EGFR activating mutations, front line therapy with gefitinib or erlotinib is the best therapeutic choice we can offer today to our patients, irrespective of their ethnicity. Conversely, for patients with EGFR wild type tumors or with unknown EGFR status, last generation platinum based chemotherapy still remains the standard of care.

References


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