EDITORIAL

Afatinib as first-line treatment for patients with advanced non-small-cell lung cancer harboring EGFR mutations: focus on LUX-Lung 3 and LUX-Lung 6 phase III trials

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Non-small-cell lung cancer (NSCLC); afatinib; epithelial growth factor receptor (EGFR); tyrosine kinase inhibitor (TKI)

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In patients with advanced or metastatic non-small-cell lung cancer (NSCLC) carrying epidermal growth factor receptor (EGFR) positive mutations, the use of EGFR tyrosine kinase inhibitor (TKI) showed to improve survival and safety profile, when compare with standard chemotherapy. These results were reported in different randomized clinical trials with erlotinib as EURTAC and OPTIMAL (1-3), and with gefitinib IPASS, NEJ002, First-SIGNAL and the West Japan Thoracic Oncology Group Study (3-6). In these studies the median progressionfree survival was around 10-12 months. After the results of the IPASS trial, gefitinib was approved for advanced NSCLC with EGFR positive mutation in all setting of treatment in Europa and Asia; while erlotinib that received in 2005 the indication in second- and third-line treatment in patients unselected for EGFR mutations after the Br.21 trial, recently was approved by FDA for the first-line treatment in patients with NSCLC harboring EGFR mutations, based on the results of the EURTAC trial in Europe, Asia and USA.

In addiction to these interesting data, the results of LUX-Lung 3 (LL3) (7) and LUX-Lung 6 (LL6) (8) trial showed and confirm the activity of afatinib, an irreversible EGFR TKI, as front-line therapy in patients with EGFR positive mutations, compared with standard chemotherapy.

In the LL3, patients were randomly assigned, with 2:1 ratio, to receive afatinib 40 mg daily or chemotherapy with cisplatin

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and pemetrexed every 21 days. Mutation-positive patients were stratified by mutation type (exon 19 deletion, L858R, or other) and race (Asian or non-Asian). The results showed a median PFS of 11.1 months for afatinib and 6.9 months for chemotherapy (HR 0.58; 95% CI: 0.43 to 0.78; P=0.001). A pre-planned analysis of PFS in patients (n=308) with exon 19 and 21 deletions was 13.6 months for afatinib and 6.9 months for chemotherapy (HR 0.47; 95% CI: 0.34 to 0.65; P=0.001). Higher response rates were observed in afatinib groups compared with chemotherapy 69% and 44%, respectively. These efficacy data regarding afatinib in mixed population, was confirmed by LL6 trial (final results are not yet published) that compared afatinib with standard chemotherapy in Asian population were PFS was 11 vs. 5.6 months (HR 0.28; 95% CI: 0.20 to 0.39; P<0.0001). Overall, these results confirmed the efficacy of afatinib in selected patients for EGFR mutations, and overlaps the previous trials with reversible EGFR TKIs, as erlotinib and gefitinib in first-line setting.

More attention it is needed to evaluate the toxicity profile of afatinib based on the results of LL3 and LL6 trials. Diarrhea (95.2%) and skin rash (89.1%) were the most common treatment-related AEs with afatinib; discontinuation rate was 8% for patients receiving afatinib and 12% of those receiving chemotherapy. Comparing these results with those from LL6 that enrolled Chinese population, it is very interesting to underline that in this trial the incidence of toxicities was lower than LL3. It is difficult to explain this issue, and it is not simple, at this time, to understand if afatinib is better tolerated in Chinese population. Comparing these results with those of pivotal trial with gefitinib and erlotinib, these results showed a little bit of more toxicities in patients treated with afatinib, when compared with erlotinib or gefitinib. Though this results are not get along with the results of quality of life (QoL) and symptoms improvement (9). Indeed, though afatinib treatment was associated with high rate of non-hematologic AEs, as

skin rash and diarrhea, in this group of patients there were an improvement of global health status and QoL, physical role, and cognitive functioning. In addiction, in patients that received afatinib there was a delayed time to deterioration for cough and dyspnoea compare with chemotherapy arm.

In June 2013, after the results of LL3, FDA approved afatinib as front-line therapy for patients with NSCLC harboring EGFR mutations.

Nowadays we have different drugs (afatinib, erlotinib and gefitinib) available for patients with EGFR positive mutations in first-line setting, approved in Europe and USA. The survival rates of these drugs are very similar but afatinib seems to be a more potent TKI. It is need to understand deeply how to interpret the results regarding toxicity profile. Non-hematologic toxicities from EGFR TKIs present a different timing and profile comparing with those toxicities from chemotherapy. Although these three drugs showed different incidence of non-hematologic AEs, at this time there is no direct data that evaluate the response after a close and correct management.

Waiting for the result of LUX-Lung 7 trial, a head-to-head study comparing afatinib with gefitinib, now we have three TKIs available for our patients with EGFR mutation, and further analysis not only of efficacy but particularly for safety profile are needed.

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