Afatinib for lung cancer: let there be light?

In the past decade the knowledge of intrinsic mechanisms of lung tumorigenesis has led to the discovery of specific pathways and potential therapeutic targets (eg, EGFR, ALK, ROS1, RET) and the development of their corresponding drug inhibitors that has revolutionised treatment of patients with advanced non-small-cell lung cancer (NSCLC).[1,2]

In 2004, three groups described the presence of activating mutations in advanced NSCLC that make tumours sensitive to EGFR tyrosine kinase inhibitors (TKIs).[3] Since then, nine randomised trials including almost 1800 patients have been done, comparing chemotherapy versus TKIs for first-line treatment of a subpopulation of patients with advanced NSCLC.[4]

LUX-Lung 6 is the most recent such trial and the second to investigate the TKI afatinib.[5] In this phase 3 trial, the investigators showed a clear superiority of afatinib over cisplatin and gemcitabine in Asian patients. Afatinib doubled median progression-survival (from 5·6 months in the gemcitabine group to 11·0 months in the afatinib group) and reduced the risk of progression or death (hazard ratio [HR] 0·28, 95% CI 0·20–0·39), while clearly improving some symptoms. These results, together with those of the LUX-Lung 3 trial,[6] which compared afatinib with cisplatin and pemetrexed (progression-free survival HR 0·58, 95% CI 0·43–0·78) prove that afatinib is a valid standard option for first-line treatment of patients with *EGFR*-mutated NSCLC. Together, these two studies should end debate about whether to start treating these patients with EGFR TKIs or chemotherapy.

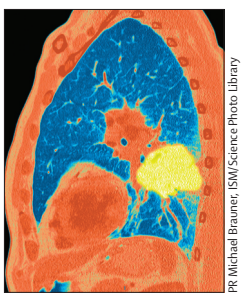
Nevertheless, some fundamental questions remain unanswered. Oncologists have had great hope for afatinib because of its peculiar ability to irreversibly inhibit all ErbB family receptor tyrosine kinases. Preclinical studies[7] suggested that afatinib could also inhibit survival of lung cancer cells harbouring a Thr790Met mutation, which is thought to be responsible for most acquired resistance to erlotinib and gefitinib, making afatinib a more appealing and efficient treatment of choice than first generation TKIs. However, LUX-Lung 3 did not directly address the effect of afatinib on patients with uncommon mutations such as Thr790Met. Rather, the results showed that when patients with rare mutations were excluded, progression-free survival in the afatinib group increased from 11·1 months to 13·6 months. Furthermore, the derived HR for progression-free survival of patients without rare mutations (1·82, 95% CI 0·85–3·87), suggests a possible detrimental effect. By contrast, in LUX-Lung 6 the HR for progression-free survival of the 40 patients who had uncommon mutations suggests that afatinib has no significant effect in this group (0·55, 95% CI 0·22–1·43).

Therefore, because data are scarce and results controversial,[8] the question of how to treat patients with uncommon mutations remains unanswered and—in the absence of robust evidence—our opinion is that chemotherapy should remain the standard of care.

A second unanswered question is the role of afatinib in treatment of non-Asian patients. LUX-Lung 6 included only Asian patients and all efficacy data for non-Asian patients is based on only 96 patients included in LUX-Lung 3. No further data were reported according to ethnic origin. This lack of information precludes the definition a risk–benefit profile of afatinib for non-Asian patients. Direct extrapolation is problematic because a meta-analysis[9] suggests that the effect of EGFR TKIs differs by ethnic origin and different biological features can result in different toxic effects and efficacies.

A third unresolved problem is which TKI should be used of the three now available. Indirect comparisons[10] seem to indicate that afatinib has a similar effect size as do gefitinib and erlotinib, but with a different pattern of toxic effects. In the LUX-Lung studies, some toxic effects of afatinib were quite different and more severe than those of other EGFR TKIs. Particularly, in LUX-Lung 6, all grades paronychia was reported in 33% of patients (57% in LUX-Lung 3), all grade stomatitis in 52% (72% in LUX-Lung 3), and diarrhoea in 88% (95% in LUX-Lung 3).

Thus, until LUX-Lung 7 (comparing afatinib with erlotinib) and LUX-Lung 8 (comparing afatinib with gefitinib) are published, the question whether afatinib constitutes a real improvement for the first-line treatment of patients with *EGFR*-mutated NCSLC will remain unsolved. Importantly, it remains of concern that three similar drugs are available to for first-line treatment of this niche group of patients, while the question of how to treat patients after disease progression and how to overcome resistance remains unclear and without approved drugs.



PR Michael Brauner, ISM/Science Photo Library

Lancet Oncol 2014

Published Online
January 15, 2014
http://dx.doi.org/10.1016/S1470-2045(14)70002-6

See Online/Articles
http://dx.doi.org/10.1016/S1470-2045(13)70604-1

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