Targeted therapies: detrimental treatment for nonsmall cell lung cancer without driver mutations

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Targeted therapies are detrimental in patients with wild-type tumours fit for conventional chemotherapy http://ow.ly/MTgy8

The search for oncogenic driver mutations is currently a standard in the management of advanced nonsquamous nonsmall cell lung cancer (NSCLC) [1], at least for epidermal growth factor receptor (*EGFR*) activating mutations and anaplastic lymphoma kinase (*ALK*) rearrangement. At the beginning of the 21st century, two small orally available molecules with EGFR tyrosine kinase inhibitor (TKI) activity, erlotinib and gefitinib, have been developed and tested mainly in unselected Caucasian populations, concomitantly or sequentially with chemotherapy. Five randomised phase III trials did not demonstrate any supplemental activity by adding the TKI to a conventional platinum-based chemotherapy [2–6]. After these disappointing data, additional research showed that these small molecules had a major activity in the presence of *EGFR*-activating mutations [7, 8]. Multiple randomised trials have now confirmed that first-generation (erlotinib, gefitinib) or second-generation (afatinib) TKIs are more active than platinum-based chemotherapy in terms of response rate and progression-free survival, while their impact on overall survival remains debatable, probably because of the large crossover noted in those trials [9–14].

Conversely, in the absence of driver mutations, EGFR-TKIs are of very limited interest. In a well-designed academic phase III trial [15], 222 patients with *EGFR* wild-type NSCLC were randomised to receive either salvage erlotinib or docetaxel after failure of first-line platinum-based chemotherapy. All evaluation criteria were inferior for erlotinib: response rate 3% *versus* 15.5% ($p<0.001$), median progression-free survival 2.4 *versus* 2.9 months, and median overall survival 5.4 *versus* 8.2 months (hazard ratio (HR) 0.73, 95% CI 0.53–1.00). More data have been generated by another phase III trial (Tarceva or Chemotherapy (TORCH)), which directly compared first-line erlotinib to cisplatin-gemcitabine in 760 patients unselected for their *EGFR* mutational status [16]. The authors pre-defined a crossover to the opposite regimen at progression. A large statistically significant detrimental effect on survival in the erlotinib arm was noted, with respective median survival times of 8.7 and 11.6 months (HR 1.24, 95% CI 1.04–1.47).

In the present issue of the *European Respiratory Journal*, Thomas *et al.* [17] report a phase III trial performed in an unselected Caucasian population comparing frontline therapy with a combination of erlotinib and bevacizumab to a triplet regimen combining cisplatin, gemcitabine and bevacizumab. Notably, there is a biological rationale for adding bevacizumab to erlotinib, as shown in a study of various xenografts of wild-type *EGFR* or EGFR-TKI-resistant tumour cells [18]. Although, at the molecular level, erlotinib and bevacizumab target different pathways (EGFR and vascular endothelial growth factor (VEGF)), they share both parallel and reciprocal downstream signalling mechanisms. In this study, it was demonstrated that bevacizumab may be useful for enhancing the antitumour activity of erlotinib by

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increasing the intratumoral concentration of erlotinib in some tumours that express high levels of VEGF protein. These findings justify the trial conducted by THOMAS *et al.* [17].

Except for adding bevacizumab in both arms, the design of the present German study was very similar to the TORCH trial. The results are close, showing a reduced activity of the targeted therapy in comparison with chemotherapy. Response rate (12% *versus* 36%; p=0.0001), progression-free survival (median 3.5 *versus* 6.9 months) and overall survival (median 12.6 *versus* 17.7 months; p=0.0409) all favoured conventional chemotherapy. A retrospective search for *EGFR* mutational status could be performed in 71% of the cases, which was representative of the whole population. The activity of erlotinib-bevacizumab in the *EGFR*-mutant patients, although better than for wild-type tumours, remained disappointing (response rate 25%, median progression-free survival 4.2 months) in comparison to what is generally reported in *EGFR*-mutated NSCLC. This can be explained by the presence of rare *EGFR* mutations of indeterminate sensitivity to EGFR-TKI in more than half of the cases, while the statistically nonsignificant increase in overall survival is probably due to the absence of second-line treatment in 75% of the patients treated with first-line chemotherapy. As a matter of fact, a first-line randomised phase II study with a similar design also did not show a significant advantage for progression-free survival with the combined targeted therapy erlotinib-bevacizumab in comparison to a platinum-based combination plus bevacizumab [19].

It is worthwhile to notice that in the second-line setting, the addition of bevacizumab to erlotinib was compared to erlotinib alone in 636 unselected Caucasian patients with advanced NSCLC. The combination showed no improvement in overall survival, although there was an improvement in progression-free survival and response rate. These two latter objectives were secondary and it was specified that they could only be taken into account if the primary objective (overall survival) was positive, which was not the case [20].

The accessibility of molecular biology in most developed countries and the development of cheaper sensitive techniques allowing determination of *EGFR* mutational status from small biopsies and cytology do not justify the performance of studies in unselected populations any more. Given the extent of high-quality evidence now published, it seems unethical to propose EGFR-TKIs in patients with wild-type tumours fit for conventional first- and second-line chemotherapy, while their use in an intercalated way with chemotherapy remains in the research domain [21, 22].

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