Front-line therapy in lung cancer with mutations in *EGFR*

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Large randomised phase III trials conducted in patients with non-small-cell lung cancer (NSCLC) harbouring activating mutations in *EGFR* have demonstrated that erlotinib or gefitinib are superior to platinum-based chemotherapy. Zhou and colleagues have now confirmed that these agents represent the best treatment we can offer today as front-line therapy for *EGFR*-mutant NSCLC.

During the past few years, treatment of metastatic non-small-cell lung cancer (NSCLC) – the leading cause of cancer-related deaths worldwide – has changed dramatically. For decades we have treated all patients with NSCLC with chemotherapy, without any clinical or biological selection and, inevitably, with disappointing survival results. Today, we know that patient selection is crucial for providing appropriate treatment and that stratification based on histology and *EGFR* status is mandatory before starting a front-line therapy. Results from large phase III trials have demonstrated that the best treatment option for patients harbouring activating *EGFR* mutations – mainly represented by deletion in exon 19 or the L858R substitution in exon 21 – is tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib that are directed towards the tyrosine kinase domain of EGFR. By contrast, for patients with wild-type *EGFR* tumours, platinum-based chemotherapy – including pemetrexed and bevacizumab or a combination of platinum with gemcitabine, vinorelbine or taxanes – remains the gold standard in non-squamous histology and squamous histology, respectively. The efficacy of EGFR TKI therapy in patients harbouring *EGFR* mutations has been confirmed in a recently published trial conducted in China, which compared erlotinib with the combination of carboplatin and gemcitabine.[1]

Only a few years ago, some investigators were convinced that an EGFR TKI could be given as front-line therapy without an *EGFR* mutation assessment.[2] Prospective phase II trials with gefitinib or erlotinib showed that these agents had a response rate in unselected patients of approximately 10%, with a median progression-free survival (PFS) of two to three months and median overall survival of 10–12 months.[3] Although response rate and PFS results were clearly inferior when compared with historical data of platinum-based chemotherapy, median survival seemed comparable to standard chemotherapy. These data supported the hypothesis that an EGFR TKI could be given as front-line therapy in an unselected population because even if the patient was

nature REVIEWS CLINICAL ONCOLOGY
This article was first published in ***Nature Reviews Clinical Oncology*** on 30 August 2011, and is published with permission. © 2011 Nature Publishing Group. doi:10.1038/nrclinonc.2011.135, www.nature.com/nrclinonc

not sensitive to the targeted therapy, platinum-based chemotherapy could be given as salvage therapy. Two phase III randomised trials have compared erlotinib with chemotherapy in chemotherapy-naive and unselected patients with NSCLC.[2,4] In the TORCH trial,[2] unselected patients with NSCLC were randomly assigned to receive erlotinib or platinum-based chemotherapy. The trial was designed to demonstrate non-inferiority of survival in patients receiving erlotinib versus chemotherapy as front-line therapy. However, as expected, chemotherapy had a superior response rate and PFS. Most importantly, the study clearly demonstrated that giving an EGFR TKI without any assessment of mutations in *EGFR*, translates into a detrimental effect on patient survival. More recently, Thomas et al.[4] compared erlotinib plus bevacizumab as front-line treatment versus the combination of cisplatin–gemcitabine–bevacizumab in patients with NSCLC unselected for mutations in *EGFR*. Similarly to the TORCH trial, the study demonstrated a detrimental effect on survival for patients randomly assigned to the erlotinib–bevacizumab arm.[4]

Initial studies with gefitinib and erlotinib had already shown that these agents are more effective in patients with certain clinical characteristics, such as female sex, never-smoker, adenocarcinoma histology and Asian race, likely because these characteristics are associated with the presence of mutations in *EGFR*.[5] Unfortunately, *EGFR* testing is not possible in all patients with NSCLC, mainly because of the lack of tumour tissue suitable for biomarker analyses. Therefore, a relevant clinical question is whether clinical selection based on the characteristics of the patient could replace selection based on genetically established *EGFR*-mutation status. To assess this, two phase III studies compared gefitinib with platinum-based doublets in patients with NSCLC and the previously mentioned clinical characteristics predictive for sensitivity to EGFR TKIs.[6,7] In these studies (FIRST-SIGNAL and IPASS) – which included East-Asian patients with adenocarcinoma histology, who were only (FIRST-SIGNAL[6]) or mainly (IPASS[7]) never smokers – PFS improvement with gefitinib was confined to patients with activating *EGFR* mutations. At the same time, patients with wild-type *EGFR* who received chemotherapy had a significantly lower risk of progression than those who received an EGFR TKI. From the clinical point of view, that means that an EGFR TKI cannot be used as front-line therapy when *EGFR* status is unknown, even in patients who present with all the clinical predictors of EGFR TKI sensitivity.

Four studies, two with gefitinib and two with erlotinib, investigated the efficacy of front-line treatment with an EGFR TKI compared with standard chemotherapy in patients with NSCLC with proven *EGFR* mutations. The WJTOG3405 and NEJ002 trials randomly assigned chemotherapy-naive patients with NSCLC harbouring activating *EGFR* mutations to gefitinib or platinum-based chemotherapy.[8,9] In both trials, gefitinib was superior to chemotherapy according to response rate and PFS, with a more-favourable toxicity profile. More recently, Rosell and colleagues[10] presented the results of the EURTAC trial, the only available study conducted in white patients harbouring activating *EGFR* mutations. This trial assigned 174 patients with advanced-stage NSCLC from Spain, Italy and France to randomly receive erlotinib or platinum-based chemotherapy. In this study, patients treated with erlotinib had a significantly higher response rate and significantly longer PFS than the chemotherapy group.

In a recent issue of *Lancet Oncology*, Zhou et al.[1] published the results of the OPTIMAL trial, a phase III study comparing erlotinib with gemcitabine–carboplatin chemotherapy in Chinese patients with NSCLC harbouring *EGFR* mutations. The study, which included a total of 165 patients, met its primary endpoint of PFS. Patients assigned to the erlotinib arm had a significant reduction of risk of progression, with a hazard ratio of 0.16. Importantly, subset analyses showed a significant PFS benefit favouring erlotinib in all subgroups, including those classically considered to be less sensitive to EGFR TKIs (male sex, smokers, non-adenocarcinoma histology). This is a relevant finding confirming that tumour biology might be much more important than clinical factors in determining whether a patient should receive EGFR TKI therapy and that when tumour growth is sustained by a specific target, drugs effectively inhibiting such a target can be dramatically effective irrespective of any clinical characteristic. The PFS improvement observed in the OPTIMAL trial was impressive: median PFS 13.1 months for the erlotinib arm versus 4.6 months in the standard chemotherapy arm. It is possible that this huge difference is not 'real', since *EGFR*-mutant tumours are more sensitive to both EGFR TKIs and chemotherapy than *EGFR* wild-type tumours. In the IPASS trial[7] – where investigators ignored the *EGFR* status – median PFS in the chemotherapy arm was 6.3 months among patients with *EGFR* mutation, about 2 months longer than reported in the OPTIMAL trial[1] – where investigators knew the *EGFR* status of the tumours.

It is important to highlight that no phase III trial has demonstrated any improvement in overall survival for patients with NSCLC harbouring *EGFR* mutations and treated with EGFR TKIs versus chemotherapy. This result is probably because of the confounding effect of post-study therapies, because in such

trials the vast majority of patients assigned to the chemotherapy arm received an EGFR TKI as second-line or third-line therapy, with an inevitable mixed effect on survival results. This resulted in a hazard ratio for overall survival that was slightly in favour of EGFR TKIs, even though the difference was not statistically significant. This trend in the hazard ratio is of clinical relevance as it suggests that the order that patients receive the treatment could be of importance and that if a patient with mutations in *EGFR* does not receive an EGFR TKI as a front-line treatment, they might be unable to receive an EGFR TKI as second-line therapy (for example, because of rapid progression), with a potential detrimental effect on overall survival as a consequence. However, if all eligible patients receive an EGFR TKI as first-line treatment, then 100% of patients would be able to benefit from the overall survival improvements and they would still likely have the option of receiving salvage chemotherapy.

In conclusion, all available data demonstrate that in the presence of activating *EGFR* mutations, EGFR TKIs are the best option that we can offer today as front-line therapy. On the one hand, even in the absence of a proven overall survival benefit, offering an EGFR TKI as soon as possible is strongly recommended in patients with *EGFR*-mutant NSCLC. On the other hand, for patients with negative or unknown *EGFR* mutation status, platinum-based chemotherapy remains the standard of care, with cisplatin–pemetrexed being the most active regimen in patients with non-squamous histology.

Details of the references cited in this article can be accessed at www.cancerworld.org

Practice point

EGFR tyrosine kinase inhibitors are the standard first-line therapy for patients with metastatic non-small-cell lung cancer who harbour activating *EGFR* mutations.

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