Editorial

# Chemotherapy plus intercalated or continuous EGFR-TKI in advanced non-small cell lung cancer

**Antonio Rossi**

Division of Medical Oncology, "S.G. Moscati" Hospital, Avellino, Italy

*Correspondence to*: Antonio Rossi, MD. Division of Medical Oncology, "S.G. Moscati" Hospital, Contrada Amoretta, 8, 83100 Avellino, Italy. Email: arossi_it@yahoo.it.

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Non-small cell lung cancer (NSCLC) accounts for more than 85% of all new lung cancer diagnoses every year worldwide (1). Most of the new NSCLC diagnoses are made when the disease is metastatic. In this stage of disease, systemic therapy is the cornerstone of treatment. In the last few years, the growing knowledge of the biologic mechanisms of NSCLC has led to the discovery of target molecules which can be inhibited by corresponding new biologic drugs. To date, in the clinical practice, about 20% of NSCLC Caucasian patients have a druggable target: activating mutations of epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*) translocations, and proto-oncogene receptor tyrosine kinase (*ROS1*) rearrangements (2). Gefitinib and erlotinib, both EGFR-tyrosine kinase inhibitors (TKIs), were investigated in combination with platinum-based chemotherapy in clinical and biologic unselected advanced NSCLC patients. Four randomized phase III trials addressed this issue and the addition of these EGFR-TKIs to chemotherapy failed to improve any outcome versus chemotherapy alone (3-6). However, the discovery of activating *EGFR* mutations and their pharmacologic inhibition by EGFR-TKIs such as gefitinib, erlotinib, icotinib and afatinib, has dramatically improved the outcomes of this subgroup of advanced NSCLC patients with a median overall survival (OS) exceeding 24 months leading to consider these drugs as the standard-of-care for this specific oncogene-addicted group (7,8).

A retrospective analysis of the TRIBUTE trial, comparing first-line erlotinib plus carboplatin plus paclitaxel versus placebo plus chemotherapy, evaluated the role of *EGFR* mutations which were identified in 29 (12.7%) of 228 patients for whom adequate tumor tissue was available. Among patients with *EGFR*-mutant tumors, 53% of those treated with erlotinib plus chemotherapy achieved an objective response rate (ORR) *vs.* 21% of those treated with chemotherapy plus placebo (P=0.13), with a median time to progression (TTP) of 12.5 *vs.* 6.6 months (P=0.092), respectively. Combining all the patients with *EGFR*-mutant tumors, regardless the treatment received, the median TTP was 8 *vs.* 5 months for those without mutations (P<0.001). Thus, in this trial, *EGFR* mutations were a positive prognostic factor for both treatments with no advantages for the addition of erlotinib (9). Despite this was a retrospective analysis with a small number of patients analyzed, the results seemed to confirm the lack of advantage from the continuous administration of EGFR-TKI in combination with chemotherapy also in *EGFR* mutated NSCLC patients. In fact, another retrospective analysis from the FASTACT-2 phase III trial comparing intercalated first-line erlotinib or placebo plus gemcitabine/platinum chemotherapy followed by maintenance erlotinib or placebo, showed, in the 256 patients for whom NSCLC tumor samples were available, that activating *EGFR* mutations were predictive for improved treatment outcomes with the intercalated regimen of chemotherapy and erlotinib (10).

The continuous administration of an EGFR-TKI and chemotherapy was hypothesized to be responsible for the

negative results of phase III randomized trials (3-6). The G1 cell-cycle arrest caused by EGFR-TKIs might reduce the cell-cycle phase-dependent activity of chemotherapy (11-13) with preclinical data showing that sequential, intercalated administration of EGFR-TKIs after chemotherapy might be effective (14-16). These preclinical data became the proof-of-concept for the clinical trials in which an intercalated regimen, consisting of the sequential administration of chemotherapy and gefitinib or erlotinib on different days of each cycle of therapy, was investigated. A recent meta-analysis pooled the data from randomized trials comparing intercalated EGFR-TKI plus chemotherapy *vs.* chemotherapy alone in any line of treatment. A total of ten randomized phase II and III trials for a total of 1,408 patients were included. Six trials investigated erlotinib, and four gefitinib, with intercalated chemotherapy. The *EGFR* mutational status was known in only 39% of patients, and 43% were *EGFR*-mutated. The primary endpoint of the meta-analysis was OS which was significantly more in favor of the intercalated combination than chemotherapy [hazard ratio (HR), 0.82; 95% confidence interval (CI), 0.71–0.95; P=0.01]. Secondary endpoints, also in favor of the combination, included progression-free survival (PFS) (HR, 0.60; 95% CI, 0.53–0.68; P<0.00001), and ORR [odds ratio (OR), 2.70; 95% CI, 2.08–3.49; P<0.00001]. These advantages were confirmed also when considering only first-line trials or only *EGFR* mutation-positive patients. The main toxicity differences were increased grade ≥3 skin rash (5.8% *vs.* 0.2%; OR, 34.22; 95% CI, 4.66–251.10; P=0.0005), and diarrhea (2.6% *vs.* 0.9%; OR, 2.99; 95% CI, 1.08–8.28; P=0.035) showed by the addition of the EGFR-TKI to chemotherapy respect to chemotherapy alone (17). Another meta-analysis pooled the data from four randomized clinical trials, for a total of 575 patients, comparing intercalated EGFR-TKI and chemotherapy versus the EGFR-TKI. There was a significant PFS improvement in favor of combination therapy (HR, 0.75; 95% CI, 0.62–0.91; P=0.004) but with no significant improvement in OS (HR, 0.87; 95% CI, 0.70–1.08; P=0.218) (18).

In August 2016, in the *Journal of Clinical Oncology*, Cheng and colleagues (19) presented the results of a phase II randomized trial, enrolling *EGFR* mutation-positive chemotherapy-naive Asiatic advanced non-squamous NSCLC patients, with a 2:1 ratio, to receive concurrent pemetrexed, at the dose of 500 mg/m$^2$ on day 1, every 3 weeks, plus continuous gefitinib, at the dose of 250 mg/day (n=129), versus gefitinib alone (n=66). The primary end point was PFS, secondary end points were TTP, OS, ORR, duration of response and toxicity. Most of the patients were women, never-smokers, with stage IV disease, 55% of patients had exon 19 deletions, and 39% had exon 21 L858R point mutations, only 6% had uncommon mutations. Median PFS was 15.8 months with the combination therapy versus 10.9 months in the gefitinib arm (HR, 0.68; 95% CI, 0.48–0.96; P=0.029). The median TTP was 16.2 months for the combination arm and 10.9 months in the gefitinib arm (HR, 0.66; 95% CI, 0.47–0.93; P=0.018). The ORR was 80% *vs.* 74% with a median duration of response of 15.4 *vs.* 11.3 months (HR, 0.74; 95% CI, 0.50–1.08; P=0.122), respectively. Analyses of all these outcomes in the main subgroups were consistent with the intention-to-treat results. OS was still immature. Grade ≥3 side effects were more frequent in the combination arm (mainly diarrhea, increased transaminases, and dermatitis acneiform in the combination arm, and diarrhea, dermatitis acneiform, and dry skin in the gefitinib-alone arm), being 42% *vs.* 19% (P=0.001), respectively, with two toxic deaths (pneumonitis and interstitial lung disease) reported in the combination arm. They concluded that the combination of pemetrexed and continuous gefitinib may offer *EGFR* mutation-positive patients a new treatment option compared with the current standard-of-care (19).

Contrary to the negative results showed by previous randomized phase III trials (3-6), why did this study report positive results with the combination of continuous gefitinib and pemetrexed?

A preclinical study investigated the combined antiproliferative effects of gefitinib and pemetrexed on EGFR-TKI-sensitive and EGFR-TKI-resistant human NSCLC cell lines. When cells were concurrently exposed to pemetrexed and gefitinib, cytotoxic synergism was reported in the gefitinib-resistant PC9/GR human NSCLC cell line due to the decrease of the levels of phosphorylated AKT, phosphorylated extracellular-signal-regulated kinase and B-cell lymphoma 2 as compared with those in the control. Antagonistic interactions were observed in the gefitinib-sensitive PC9 cell line due to the gefitinib-induced G0/G1-phase blockade, which interfered with the cell cycle-specific cytotoxicity of chemotherapy. This study suggested that EGFR-TKIs combined with pemetrexed may be a beneficial treatment strategy for NSCLC patients with acquired resistance to EGFR-TKIs (12).

The results of this preclinical study are in contrast with the clinical ones. First-line combination of pemetrexed and gefitinib scored better than gefitinib in advanced

 

NSCLC harboring sensitive *EGFR* mutations (19), while, in the IMPRESS trial, the combination of gefitinib plus cisplatin plus pemetrexed did not improve PFS, the primary endpoint, compared with chemotherapy in *EGFR* mutated NSCLC patients with acquired resistance to first-line gefitinib (20). This last negative clinical result could be further explained also by the fact that in most *EGFR* wild-type or sensitizing-mutant NSCLC cells, the concomitant administration of gefitinib and cisplatin showed antagonism, due to the interference of gefitinib with cisplatin entry into the cell (21). This consideration could be a further potential explanation for the failure of the concomitant administration of gefitinib or erlotinib with platinum-based chemotherapy in previous randomized trials (3-6). Moreover, a further preclinical study reported that gefitinib-treated EGFR-TKI-sensitive NSCLC cells showed a wide spectrum of chemo-refractoriness (16). These results, suggesting that concomitantly combined EGFR-TKI plus chemotherapy might not be a good treatment strategy for NSCLC harboring sensitizing-*EGFR* mutation, are completely opposed to what reported by the previous preclinical study (12). Other preclinical studies suggested that the sequence of chemotherapy followed by EGFR-TKI may be superior to other sequences in treating NSCLC cell lines (14,15). Unfortunately, there are several contrasting preclinical and clinical results difficult to interpret, and no clear conclusions and answers can be drawn.

In the trial by Cheng and colleagues (19), only patients with performance status (PS) 0–1 were randomized. Both gefitinib and pemetrexed showed activity and safety also when administered to PS 2 patients (22-24). This study, including only *EGFR* mutated NSCLC patients, had to be open also to the enrollment of PS 2 patients to investigate if the combination therapy could improve outcomes of this poor prognosis subgroup, too. The authors concluded that this trial provided a new potential treatment option, the combination of pemetrexed and gefitinib, for patients with *EGFR* mutation-positive NSCLC. However, this conclusion has to be confirmed by OS results, still pending, and in further randomized phase III trials before considering this combination as a new standard-of-care for this oncogene-addicted NSCLC patients. In this scenario, the combination of erlotinib and bevacizumab already demonstrated, in a phase II randomized trial, to improve the results of erlotinib alone, in the same oncogene-addicted NSCLC patients (25). Moreover, the use of this combination is based on a strong and clear preclinical rationale and further confirmatory randomized phase III trials are ongoing (26).

Overall, we have several subgroups of patients based on the *EGFR* status (mutated, wild-type and unknown), the line of therapy (first, and second), ways to combine EGFR-TKI and chemotherapy (continuous, intercalated, and sequential). Unfortunately, independently of patients' characteristics and setting, and despite the initial activity, an acquired resistance to these EGFR-TKIs arises, pointing out the issue of further treatment choice based on the presence or not of the acquired *EGFR* mutations of resistance T790M against which third-generation EGFR-TKIs are highly active (3).

In conclusion, there is absence of clear preclinical and clinical information on the best way to combine EGFR-TKIs and chemotherapy in both EGFR-mutated and wild-type NSCLC cell lines and patients. Overall, the results are interesting enough to promote further preclinical studies and well-designed randomized trials, including both continuous and intercalated EGFR-TKIs plus chemotherapy combinations, in first- and second-line therapy, and regardless the *EGFR* status, to obtain better evidence in this setting and to give a clearer answer to the title question.

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