Commentary

A potential new therapeutic option for patients with advanced EGFR mutation-positive non-small cell lung cancer in first-line setting

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EGFR mutation-positive non-small cell lung cancer (NSCLC) is a well-defined molecular subtype of lung cancer. We already know data on frequency and characteristics of EGFR mutations among patients with NSCLC and their response to tyrosine kinase inhibitors (TKIs) (1). Actually these small molecules represent the standard first-line treatments for this setting of patients, while platinum-based doublet chemotherapy is the standard first-line treatment for patients with wild type EGFR NSCLC (2).

Gefitinib, an orally active, selective and reversible EGFR-TKI, had been largely studied and developed for treatment in first-line setting of patients with advanced EGFR mutation-positive NSCLC compared with chemotherapy (3,4) both in Caucasian and non-Caucasian patients (5-7).

Pemetrexed is a potent inhibitor of folate-dependent enzymes involved in the *de novo* biosynthesis of thymidine and purine nucleotides, essential for cell replication. *In-vitro* studies had shown that pemetrexed inhibits glycinamide ribonucleotide formyltransferase (GARFT), dihydrofolate reductase (DHFR), thymidylate synthase (TS) (8).

Pemetrexed was firstly approved for second-line treatment as a single agent (9) then in first-line setting in association to cisplatin for the treatment of NSCLC patients with non-squamous histology, on the basis of the JMDB study (10).

We also know that low TS expression is a predictive factor for pemetrexed efficacy and that gefitinib suppresses the expression of TS in NSCLC cell lines, independently from *EGFR* status. Thus the addition of pemetrexed to first-line treatment with gefitinib may increase its efficacy (11,12).

On this basis, Cheng and colleagues (13) conducted a randomised phase II trial to determine whether in first-line setting the addition of pemetrexed to gefitinib could provide a clinical benefit compared with gefitinib alone for patients with advanced EGFR mutation-positive non-squamous NSCLC. All patients were from East Asia with a histologically or cytologically confirmed diagnosis of NSCLC in advanced-stage with a common EGFR mutation (*exon 19* deletion or *exon 21 Leu858Arg* point mutation). They were randomised at a ratio of 2:1 to receive pemetrexed 500 mg/m^2 in intravenous infusion on day 1 every 3 weeks and oral gefitinib (250 mg) once per day continuously or gefitinib alone. Patients received treatment until disease progression, unacceptable toxicity, or other study discontinuation criteria.

Primary endpoint of the trial was progression-free survival (PFS), while secondary endpoints were time to progressive disease (TtPD), overall survival (OS), tumor response rates, duration of response (DoR), and safety.

One hundred and twenty-nine patients were enrolled in pemetrexed plus gefitinib arm and 66 patients in gefitinib alone arm. Sixty-five percent of patients in pemetrexed plus gefitinib arm and 63% of patients in gefitinib arm were women. The majority of patients were younger than 65 years and never-smokers. In each study arm patients with *exon 19* deletion were more represented than those with *exon 21 Leu858Arg* point mutation. In particular in pemetrexed plus gefitinib arm patients with *exon 19* deletion were 52% and those with *exon 21 Leu858Arg* mutation were 41% respectively, while in gefitinib arm they were 62% and 35% respectively.

All patients receiving at least one administration of study drug composed the intention to treat (ITT) population and they were included in the efficacy and safety analyses.

Median PFS in pemetrexed plus gefitinib arm was significantly higher compared with that in gefitinib arm (15.8 *vs.* 10.9 months; HR, 0.68; P=0.029), and the advantage of combined therapy was reported both for patient with EGFR *exon 19* deletion and *exon 21 Leu858Arg* mutation (median PFS 17.1 *vs.* 11.1 months in *exon 19* deletion subgroup and 12.6 *vs.* 10.9 months in *Leu858Arg* point mutation subgroup). This finding confirmed the evidence of previous literature supporting a better outcome with first generation TKIs for patients with NSCLC harbouring an *exon 19* deletion as EGFR mutation (14,15), suggesting that *exon 19* deletion and *exon 21 Leu858Arg* point mutation define two distinct forms of NSCLC.

TtPD was longer with pemetrexed plus gefitinib than with gefitinib alone too. TtPD was 16.2 versus 10.9 months, respectively (HR, 0.66; P=0.018). Data about OS were immature at time of analysis.

The objective response rates (ORRs) were 80% in pemetrexed plus gefitinib arm and 74% in gefitinib arm, with no statistical significant difference. The disease control rates (DCRs) were similar between the two study arms too (93% and 94% respectively), with a greater number of stable disease in gefitinib arm.

The median DoR was analysed in the ITT population that reached a complete or a partial response. It was 15.4 months for pemetrexed plus gefitinib arm and 11.3 months for gefitinib arm.

Similar findings were reported in a small Japanese phase II trial including 26 patients with advanced EGFR mutation-positive NSCLC who received in first-line setting treatment with pemetrexed and gefitinib (16). Patients' characteristics deviated from the typical ones of similar studies. In effect the majority of patients were *Leu858Arg* mutation-positive, 50% of patients were women and 54% were current or ex-smokers. In this study the authors reported an ORR of 84.6% and a DCR of 96.2%, with a median PFS of 18.0 months. The advantage was reported both for patients with *exon 19* deletion positive and patients with *Leu858Arg* mutation-positive NSCLC, with a tendency to be more effective in tumor with *exon 19* deletion, similarly to the results of a recent meta-analysis (15).

Moreover several studies investigated whether the addition of a TKI to chemotherapy both in first and second line of treatment could provide an efficacy advantage. INTACT-1 and INTACT-2 trials evaluated the addition of gefitinib to first-line cisplatin plus gemcitabine and carboplatin plus paclitaxel, respectively. Both studies concluded that gefitinib did not provide any advantage in terms of survival (17,18). Other studies on TKIs in first-line setting in addition to a platinum based chemotherapy demonstrated no benefit both in PFS (19) and survival (20).

These negative findings were explained by the action of EGFR-TKIs and chemotherapeutic agent in different cell cycle phases. In effect EGFR-TKIs cause G1 cell cycle arrest, while cytotoxic chemotherapies act on dividing cells. So the arrest of cell cycle in G1-phase protects cells from the cytotoxic effects of cell cycle phase-dependent chemotherapeutic agents (21,22).

On the contrary, sequential administration of EGFR-TKIs following chemotherapy has been shown to provide greater efficacy than concurrent administration (23,24).

On this basis several studies of different and sequential combinations of drugs were conducted, as the FAST-ACT phase II study (25) and the subsequent FASTACT-2 (26), a multicentre, randomised, placebo-controlled, double-blind, phase III study of intercalated erlotinib or placebo with gemcitabine and carboplatin or cisplatin for six cycles, followed by maintenance with erlotinib or placebo in Asian patients with advanced NSCLC. In this trial PFS was significantly higher with chemotherapy plus erlotinib compared with chemotherapy plus placebo (7.6 *vs.* 6.0 months; HR, 0.57; P<0.0001). OS was longer too (18.3 *vs.* 15.2 months, respectively). The benefit was more evident among patients with an EGFR mutation-positive NSCLC, with a median PFS of 16.8 *vs.* 6.9 months (HR, 0.25; P<0.0001) and a median OS of 31.4 *vs.* 20.6 months (HR, 0.48; P=0.0092). The investigators concluded that this intercalated treatment is an option for EGFR mutation-positive NSCLC and for patients with unknown EGFR status too, but this trial was conducted among Asian patients, who presented a higher rate of EGFR mutations (27).

It should be stressed that all these mentioned trials were conducted in a population of patients unselected *a priori* for EGFR mutational status. Furthermore no benefit was reported also in IMPRESS trial, where patients who progressed after first-line treatment with gefitinib received cisplatin plus pemetrexed associated to gefitinib or placebo, to overcome the acquired resistance to EGFR-TKI (28).

Therefore the study of Cheng and colleagues (13) is the first randomised trial evaluating concurrent pemetrexed and gefitinib as first-line treatment in NSCLC patients selected for histology and EGFR status.

The significant better PFS in pemetrexed plus gefitinib

group increases with time as demonstrated by the progressive separation of curves with time in the ITT population. Regarding clinical characteristics, the PFS advantage with pemetrexed plus gefitinib was better among women and never smokers as expected for the efficacy of a TKI. Moreover patients who had received a prior adjuvant or neoadjuvant treatment showed a higher PFS too.

Considering the adverse events (AEs) the majority of them were of grade 1 or 2. However 42% of patients in pemetrexed plus gefitinib arm experienced AEs of grade ≥3 compared with 19% of patients in gefitinib arm. The most commonly reported AEs were diarrhea, increased serum level of ALT and AST and dermatitis acneiform in pemetrexed plus gefitinib arm, diarrhea, dermatitis acneiform and dry skin in gefitinib arm. Two patients in pemetrexed plus gefitinib arm and one patient in gefitinib arm reported interstitial lung disease.

The trial presented the limitation due to the immature data on OS precluding robust analysis.

Although no benefit in OS was reported in this trial in first-line setting, the association of pemetrexed and gefitinib might be more effective than gefitinib alone, in terms of PFS.

The study reported very prolonged PFS. Until now in patients with EGFR mutation-positive advanced NSCLC previous trials had reported median PFS of 9.6 months for gefitinib alone (29) and recently 11 months for the irreversible ErbB family blocker afatinib (30).

However the trial showed also an increased but manageable toxicity profile for pemetrexed plus gefitinib arm, similar response rates and DCR between the two arms. So it is to be evaluated the risk-benefit ratio considering the findings of the trial and all the clinical relevant endpoints such as disease control, survival prolongation, tolerability and quality of life. These factors are to be taken into account to choose the most appropriate treatment for every patient.

Moreover this trial included only East Asian patients. It could be investigated if the advantage in PFS remains in EGFR mutation-positive Caucasian patients too.

It would be interesting to study whether the association of pemetrexed and gefitinib could delay the onset of the acquired resistance to TKIs, designing future trial about combination approaches and/or sequence strategy.

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Footnote

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