Editorial

Second-line treatment in EGFR-unselected patients: is it time to close one arm of this river's DELTA?

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Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related death worldwide. Despite advances in treatment, most patients will eventually relapse. Nowadays, there are four monotherapy options available for second-line standard treatment for patients with stage IV NSCLC: pemetrexed (for non-squamous NSCLC), docetaxel, erlotinib or gefitinib (1,2). Current practice guidelines do not require epidermal growth factor receptor (EGFR) mutation status testing before initiating a second-line therapy with an EGFR tyrosine kinase inhibitor (TKI).

As oncologists, our main goals are to improve quality of life and symptoms as well as to increase survival with the least toxicity possible. At the beginning of this century, Docetaxel was accepted as second-line therapy in advanced NSCLC following two clinical trials demonstrating better symptom control, quality of life and improved survival when compared to best supportive care (3,4).

Erlotinib has been proven to be superior to placebo both in terms of quality of life and survival. This benefit was unrelated to EGFR-mutation status (analyzed by immunohistochemistry) (5), whilst patients treated with gefitinib have a non-inferior outcome when compared to docetaxel (6).

In general, trials of EGFR TKIs in molecularly unselected patients have shown similar survival outcomes when compared to chemotherapy. What is more, in two trials conducted in molecularly unselected Asian populations, better progression-free survival (PFS) was seen with the use of EGFR TKIs (7,8). Nevertheless, it should be taken into account that EGFR mutations are more common in Asians.

The question of whether it is better to offer a TKI for second-line treatment in patients with wild-type EGFR instead of chemotherapy has long gone unanswered; to date, findings among trials have not been consistent. In the INTEREST (IRESSA NSCLC Trial Evaluating Response and Survival Against Taxotere) study, no significant differences were found in overall survival (OS) or PFS between second-line treatment with docetaxel or gefitinib. In this trial, EGFR-mutation status was retrospectively identified (9). On the other hand, the TAILOR (Tarceva Italian Lung Optimization Trial) trial (1), a prospective randomized controlled study with EGFR wild-type NSCLC patients, was the first study to show that chemotherapy with docetaxel was more effective than erlotinib as second line treatment in this population both in terms of OS and PFS. A survival benefit of almost three months was found in patients receiving chemotherapy rather than erlotinib (8.2 *vs.* 5.4 months).

The Docetaxel and Erlotinib Lung Cancer trial (DELTA) (10) was performed in molecularly unselected patients, randomizing them to treatment with either docetaxel or erlotinib in the second-line setting. In this trial, the EGFR mutation was not determined in the whole study population despite one of the primary aims being to determine the efficacy of TKIs *vs.* chemotherapy in this population.

Table 1 Overall and progression free survival in DELTA and TAILOR trials

Treatment (n)	DELTA		TAILOR	
	Erlotnib150 (109 WT*)	Docetaxel 151 (90 WT*)	Erlotinib 112 (110 included)	Docetaxel 110
OS (months)	9.0	10.0	5.4	8.2
PFS (months)	1.3	2.9	2.4	2.9

*In the subset analysis. Abbreviations: OS, overall survival; PFS, progression-free survival.

Instead the authors performed a subgroup analysis by EGFR mutation status. In this subgroup analysis EGFR-wild type NSCLC patients receiving treatment with docetaxel had a superior PFS compared to those receiving erlotinib (2.9 *vs.* 1.3 months). Nevertheless, contrary to the findings of the TAILOR trial—where EGFR mutation status was prospectively determined in the whole study population (1)—no significant differences were found regarding OS. This trend was seen in 2008 in the V15-32 trial, where non-inferiority in OS between patients treated with docetaxel and gefitinib was not demonstrated (11).

Interestingly, responses to *EGFR TKIs* in *EGFR* wild-type NSCLC patients were seen in both the DELTA and the TAILOR trials (5.6% and 3%, respectively) (*Table 1*) (1,10). These findings emphasize the need to standardize EGFR testing methods since potential bias from false-negative, and even false-positive, results may occur. Not to be forgotten is the growing evidence showing the existence of *de novo* resistance mutations in NSCLC patients which could influence outcome in these patients.

In accordance with these results, genotyping for NSCLC should be considered mandatory even in the second-line setting, before administration of EGFR TKI. It is time to ask ourselves whether it is beneficial to continue offering EGFR TKIs in second line to non-mutated patients.

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