CURRENT ONCOLOGY
A Canadian Cancer Research Journal

Second-line treatment of non-small-cell lung cancer with wild-type *EGFR* status. What is the best approach?

The Editor
Current Oncology
31 August 2015

We read with great interest the article of Ma and colleagues titled "An exploratory comparative analysis of tyrosine kinase inhibitors or docetaxel in second-line treatment of *EGFR* wild-type non-small-cell lung cancer: a retrospective real-world practice review at a single tertiary care centre"[1]. The authors presented a retrospective cohort study including patients with *EGFR* wild-type non-small-cell lung cancer (NSCLC) who received tyrosine kinase inhibitor (TKI) as second- or third-line therapy, and they compared clinical outcomes for TKI and single-agent docetaxel in second-line treatment.

In the article, the authors concluded that second-line therapy with TKI for *EGFR* wild-type NSCLC (compared with docetaxel) was associated with statistically better progression-free survival (PFS) and event-free survival, and noninferior overall survival. That finding is quite surprising and might be related to the many limitations of the study. Indeed, in addition to the limitations reported by the authors (the relatively small size of the cohort, the selection bias, the variability in the timing of imaging, and the retrospective nature of the analysis), we can make several comments.

First, considering the results of two large randomized phase III trials (DELTA and TAILOR)[2,3] and a meta-analysis[4], it is now well established that chemotherapy is better than erlotinib in terms of PFS in the second-line treatment of NSCLC with wild-type *EGFR* status. It is difficult to consider the results of a retrospective study such as that in the article from Ma and colleagues rather than those from the more methodologically strong studies.

Second, Ma *et al.* did not specify in the article how they defined *EGFR* wild-type patients. That information is important, because if the authors excluded only patients with classical *EGFR* mutation (exon 19 deletion and L834R substitution mutations), it is possible that some patients classified as *EGFR* wild-type in the study might have some rare activating *EGFR* mutations (non-classical mutations in exons 18–21).When receiving TKIs, those patients might consequently achieve a longer PFS than do those with true *EGFR* wild-type mutations, thus leading to a better PFS than is seen in patients receiving docetaxel. Furthermore, the detection method used for the *EGFR* mutation analysis (not reported in the study) might also have affected the study results, because the currently available methods have different sensitivities and specificities[5].

Third, the treatment-free interval after the prior line of chemotherapy is another important parameter to take into consideration. Indeed, Odabas*et al.*[6] recently reported that the time elapsed after first-line treatment (≥3 months vs. <3 months) was an independent prognostic factor. In their article, Ma *et al.* did not provide information about treatment-free interval before start of second-line treatment, which might not lead to an accurate assessment of survival.

For all the above reasons, we suggest that docetaxel is more effective than erlotinib for the second-line treatment of NSCLC with wild-type *EGFR* status, and that the study finding is probably the result of the many limitations of the study. Also, we believe that neither docetaxel nor erlotinib are miracle solutions for the second-line treatment of previously treated patients with NSCLC who have wild-type *EGFR* tumours. To improve outcomes for such patients, some recently approved approaches include chemotherapy and targeted-therapy combinations (docetaxel plus ramucirumab, docetaxel plus nintedanib) and immunotherapy (nivolumab).

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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