TKIs in NSCLC: the down of a new era?

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The understanding of the molecular pathology of carcinogenesis in non-small cell lung cancer (NSCLC) has led to the development of targeted agents. One of the most profoundly investigated pathways is that of the epidermal growth factor (EGF) and its receptor (EGFR). In our days we have two types of inhibitors of EGFR, one being the extra-membrane and the other, the intra-cellular tyrosine kinase domain (EGFR-TKIs). The initial studies with EGFR-TKIs, gefitib and erlotinib, had demonstrated that a small proportion of unselected patients with NSCLC showed a great response to these agents. It took more than 5 years to understand the reason for this response. A large and confusing body of small or retrospective molecular studies were published in order to evaluate if the EGFR expression by immunohistochemistry (IHC) or the EGFR copy number by in situ hymbidiazation (FISH) can predict response to the new agents before actually concluding that the EGFR gene mutation status is the predominate predictive marker (1). This delay could underscore the need for quick and total shift in the design of the lung cancer trials.

The results of a prospective molecular markers analysis from the randomized *SATURN* trial were published by Brugger *et al.* (2). In *SATURN* study, it was evaluated the use of erlotinib as a switch maintenance strategy in the advanced, NSCLC patients who have responded in the first line platinum based treatment (3). This study met its primary end point of significantly prolonged progression free survival (PFS) with erlotinib versus placebo. The fact that the collection of tumor samples was mandatory allowed the prospective analyses of prognostic and predictive biomarkers.

In Brugger *et al.* study, EGFR protein expression by IHC, EGFR copy number by FISH and the presence of KRAS and EGFR mutations were evaluated for their prognostic or predictive value. The authors concluded that, although the study was underpowered for prognostic tests, *KRAS* MUT+ status emerged as a significant negative prognostic factor for PFS (HR, 1.50; 95%CI, 1.06 to 2.12; P=0.020) and, on the other hand, *EGFR* MUT+ status was a significant positive prognostic marker for OS (HR, 0.33; 95%CI, 0.19 to 0.59; P<0.001). As for the predictive contribution of the examined biomarkers to the PFS by the use of erlotinib, the interaction between treatment and EGFR IHC status, EGFR FISH status and KRAS mutation status was not significant, suggesting that there was no differential effect of erlotinib on PFS between positive and negative groups (P=0.63, P=0.35, P=0.95 respectively). On the other hand, the interaction of treatment and EGFR mutation status was significant (P=<0.001) indicating that this marker has a predictive value for PFS benefit of erlotinib switch maintenance strategy. As for the predictive contribution of biomarkers to the overall survival by the use of erlotinib, although in the ITT population of SATURN the erlotinib significantly reduced the risk of death (HR, 0.81; 95% CI, 0.70 to 0.95; P=0.0088), the current study of Brugger *et al.* was underpowed for such analysis within subgroups. The lack of translating the PFS benefit into OS benefit in patients with *EGFR* MUT+ status in Brugger's trial, can be first attributed to the fact that median OS had not been reached by the time of the analysis (only 8 events among the 22 *EGFR* MUT+ patients in erlotinib arm), secondly to the small number of *EGFR* MUT+ patients (49 among 889) and finally to the fact that OS is affected by cross over and subsequent therapies in placebo arm. Studies that strengthen the use of EGFR TKIs in front line

treatment of advanced NSCLC have also failed to show improvement in OS, with the new agents in EGFR mutated patients mostly due to cross over (4). Considering also the fact that more and effective subsequent lines of therapy are now available, the question that rises is if this is the time for us to compromise with PFS as primary end point in lung cancer trials.

This extensive prospective molecular markers analysis contributes greatly in selecting patients who can be benefited from erlotinib maintenance str (5). It is also pointing out the need for mandatory tissue sample collection and biomarker analysis in early phase non randomized trials, in order to use them for patients' selection in phase III trials. From 889 available tissue samples, EGFR mutation status was able to be detected in only 437 because for many patients only small amounts of tissue were available. Based on the unclear previous knowledge for the predictive value of EGFR expression, EGFR copy number and KRAS and EGFR mutation status, the authors prioritized the biomarkers analysis as follows: EGFR IHC, EGFR FISH, KRAS mutation status and finally EGFR mutation status. Thus, the most important biomarker was examined in only 49% of the study population. In IPASS study, which gave the green light to the other EGFR TKI gefitinib for 1st line treatment in EGFR mutant patients with NSCLC, out of the 1,217 patients eligible for randomization only 683 (52%) provided tissue samples and EGFR mutation status could be evaluated in only 437 (35.9%). This made more emerging the need for a change in trial design paradigm in lung cancer. A lateral aim should be the development of new methods that can assay new and old markers in easier collected samples like blood, bronchial washing and pleura fluid or in cytological specimens.

If we want to improve the lives of our patients we must close once and for all the era of unselected population studies and try to enlighten the era of individualizing medicine by detecting and using molecular markers in order to give the right drug to the right patient, at the right time and the right dose.

Acknowledgements

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