Research Highlight

Biomarkers in the selection of maintenance therapy in non-small cell lung cancer

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Long gone are the days where identification of lung cancer as either non-small cell lung or small cell is sufficient to initiate therapy. Today, the optimal treatment of lung cancer hinges not only on accurate histopathologic diagnosis but further tumor description through molecular characterization (1). The importance of molecular testing prior to initiation of therapy is best highlighted by epidermal growth factor receptor (*EGFR*) mutational analyses. There have been a number of trials that have identified patients who gleaned a greater benefit from *EGFR* tyrosine kinase inhibitor (TKI) therapy on the basis of *EGFR* mutation positivity in first, second and third line treatment regimens.

The results from the Spanish Lung Cancer Group demonstrated the feasibility of prospectively testing for *EGFR* mutation prior to *EGFR* TKI initiation (2). This was further supported by several phase III trials evaluating first-line therapy with *EGFR* TKIs versus platinum doublet chemotherapy in advanced NSCLC (3-8). The IPASS and First-SIGNAL trials evaluated first line gefitinib versus standard chemotherapy in patients selected based on clinical factors known to be associated with a higher prevalence of *EGFR* mutations (4,7). Planned subgroup analysis based on *EGFR* mutational status was conducted in the IPASS trial and demonstrated that those with *EGFR* mutations had a better progression free survival (PFS) with first line gefitinib than chemotherapy and those without *EGFR* mutations responded significantly better to standard chemotherapy (7). Two additional trials that only included patients with *EGFR* mutation- positive tumors (WJOTG3405 and NEJ002) had results that confirmed those from IPASS and First-SIGNAL. While gefitinib is not currently approved for use in the United States, it is routinely prescribed as first line therapy for those who are *EGFR* mutation-positive outside the U.S. The OPTIMAL phase III trial, the first to prospectively compare erlotinib (approved for use in the U.S.) with chemotherapy in patients with *EGFR* mutation-positive tumors, had similar results to the gefitinib trials with a longer PFS in those treated with the *EGFR* TKI (8). Results from the European phase III EURTAC study also demonstrated longer PFS with first-line erlotinib versus chemotherapy in patients with *EGFR* mutation-positive (9) NSCLC, further supporting the use of molecular testing prior to the initiation of therapy.

One of the questions left unanswered is whether or not molecular testing of *EGFR* receptor status is useful in the selection of maintenance therapy. In this issue of *Translational Lung Cancer Research*, a reprint of a study published in the *Journal of Clinical Oncology* by Brugger *et al.* (10) reports on the molecular analyses from the Sequential Tarceva in Unresectable Non-Small-Cell Lung Cancer (SATURN) trial (11). An important aspect of this trial was the successful collection of tissue samples for biomarker analysis in the majority of patients enrolled in the study. The study was also powered for and met both primary endpoints: improvement in PFS of all in the intention to treat group and in PFS of patients with *EGFR* positive tumors determined by IHC. In the SATURN study, PFS was prolonged for 1 month in both *EGFR* IHC positive and negative patients arguing against the use of this biomarker in selecting maintenance therapy in those with clinically stable disease. Additionally, though this was not the primary endpoint of the study, Brugger *et al.* assessed *EGFR* by mutational status using PCR and

found this method a better predictor of PFS with erlotinib maintenance therapy. Those with an *EGFR* mutation had a dramatically greater PFS benefit with erlotinib versus placebo than those with *EGFR* wild type. Future study will be needed to confirm this finding using RT-PCR testing for *EGFR*.

While this study was not designed to identify the utility of biomarkers as prognostic tests, some useful information emerged. Not surprisingly, those who were *EGFR* mutation + had an improved overall survival, while those that were found to be KRAS mutation + had a worse progression free survival.

The SATURN trial draws the conclusions that erlotinib should be a consideration as maintenance therapy in patients with NSCLC who do not progress following 4 cycles of platinum based chemotherapy, but does not suggest that erlotinib selection should be based on molecular analysis. So what is the clinical application for *EGFR* mutational testing in drug selection? Certainly there is ample evidence to support testing prior to the initiation of first line therapy and if the information is available, then an *EGFR*-TKI should be given first line to those with sensitizing *EGFR* mutations. Should an *EGFR* TKI be given as maintenance in those without *EGFR* mutations? The data from this trial is a qualified maybe as there is a statistically significant improvement in PFS of just one month without any improvement in overall survival when used as maintenance therapy irrespective of *EGFR* IHC status. Maintenance therapy in patients with NSCLC that has not progressed after first line therapy is increasingly accepted in practice and both erlotinib and pemetrexed are approved for this indication. Given the exploratory results of *EGFR* mutational testing using RT-PCR one strategy to consider when selecting maintenance therapy would be to use erlotinib in those that are *EGFR* positive by RT-PCR if they have not already received erlotinib first line therapy and pemetrexed or erlotinib in those that are *EGFR* wild type by RT-PCR. A trial comparing the two approved maintenance therapies is warranted in patients with non-squamous NSCLC who are *EGFR* mutation-negative.

Irrespective of the results of the current or future trials it has become apparent that treatment decisions in NSCLC have become increasingly individualized with a goal of personalized therapy. It is imperative to obtain adequate tissue sampling not only for histopathologic typing, but to assess biomarker status for individualized therapy. This will only become more imperative as new molecular targets for therapy are discovered.

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