Research Highlights

Highlights from the latest papers in the pharmacogenetics research of EGFR in lung cancer patients

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Gefitinib in a molecularly defined chemonaive population with advanced non-small-cell lung cancer

Evaluation of: Sequist LV, Martins RG, Spiegel D *et al.*: First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic *EGFR* mutations. *J. Clin. Oncol.* 26(15), 2442–2449 (2008).

The current standard of care in the management of patients with advanced non-small-cell lung cancer (NSCLC) using cytotoxic chemotherapy offers a very modest benefit in terms of response rates and median survival. The other treatment option involves *EGFR* blockade with tyrosine kinase inhibitors (TKIs), which is currently recommended as second line agents in NSCLC. A number of retrospective studies have suggested that patients with NSCLC harboring *EGFR* mutations may have higher response rates and median survival compared with those who were treated with chemotherapy [1,2]. This has raised questions on when to initiate *EGFR* TKI treatment and how best to select patients based on their genotypic profile.

In a Phase II multicenter study by Sequist *et al.*, 98 chemotherapy naive patients with one or more clinical characteristics associated with *EGFR* mutations underwent direct DNA sequencing of tumor tissue *EGFR* exons 18–21 [3]. The primary outcome of the study was response rate. The commonest *EGFR* mutations detected were exon 19 deletions (53%) and L858R (26%) mutations. Of the 34 (35%) patients who had *EGFR* mutations detected,

31 patients received gefitinib 250 mg/day until progression or unacceptable toxicity occurred. The median follow up was 12.3 months. The results demonstrated a significant clinical benefit with an overall response rate of 55%, a median progression free survival of 9.2 months and overall survival of 17.5 months. The toxicity profile of gefitinib was also more favorable compared with combination chemotherapy with only one patient (3%) removed from treatment owing to grade 3 pneumonitis.

The study by Sequist *et al.* suggest the usefulness of TKIs as first-line therapy in a molecularly defined chemonaive population. The study also showed that prescreening of the *EGFR* gene may identify subgroup of patients who may not respond favorably to treatment with TKI, such as those harboring exon 20 insertion mutation or amplification of the *Met* gene. However, no association was found between *EGFR* gene copy-number in mutation-positive patients and overall response rate. This is no surprise as the presence activating *EGFR* mutations are often associated with an increase in *EGFR* gene copy-number. This also brings the discussion to another important issue: should *EGFR* gene copy-number be included in the armamentarium of markers used to guide therapy with TKIs in chemonaive patients? My opinion is that inclusion of *EGFR* gene copy number will probably increase the precision of patient selection, regardless of their mutation status.

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EGFR mutational status and clinical outcome to gefitinib monotherapy in chemonaive non-small-cell lung cancer patients

Evaluation of: Yang CH, Yu CJ, Shih JY *et al.*: Specific *EGFR* mutations predict treatment outcome of stage IIIB/IV patients with chemotherapy-naive non-small-cell lung cancer receiving first-line gefitinib monotherapy. *J. Clin. Oncol.* 26(16), 2745–2753 (2008).

The tyrosine kinase inhibitors (TKIs) constitute an important class of drugs in the treatment of non-small cell lung cancer (NSCLC), especially in patients who have failed chemotherapy. Several factors are known to influence response to TKIs and include females of Asian ethnic origin, nonsmokers, adenocarcinoma pathology and good performance status. Molecular biomarkers associated with positive outcome have included the presence of activating mutations in the tyrosine kinase domain of the *EGFR* gene as well as increase in the *EGFR* gene copy-number. The presence of *Met* amplification was recently shown to be associated with acquired resistance.

Yang *et al.* recently reported that the presence of specific *EGFR* mutations, such as exon 19 deletion or L858R mutations were associated with a longer time-to-treatment failure (TTF) in stage IIIB/IV chemotherapy-naive NSCLC patients receiving gefitinib 250 mg/day [1]. The study was prospectively planned

and powered for correlative gene mutation studies. The overall response rate was 51% after a median follow-up duration of 18.3 months. Median time TTF was 5.5 months and median overall survival was 22.4 months. Patients with adenocarcinoma or deletion in exon 19 or L858R *EGFR* mutations had statistically higher response rates compared with patients with nonadenocarcinoma type tumors or harboring other types of *EGFR* mutations. Furthermore, multivariate analysis revealed the presence of *EGFR* exon 19 deletion or L858R mutations in adenocarcinoma patients to be predictive of longer TTF whilst other covariates such as sex, smoking status and tumor pathology were found not to predict for long TTF. The presence of high *Met* copy number was associated with a shorter TTF, although this was statistically nonsignificant.

This study highlights certain important issues with regard to the use of *EGFR* mutation status in predicting therapeutic outcome in patients receiving TKIs. Firstly, the specific *EGFR* mutation type may be important in predicting both the clinical response and the duration of response in chemotherapy naive NSCLC patients. Secondly, the presence of *Met* amplification may affect the duration of response to TKIs. Higher *Met* gene

copy-numbers and *KRAS* mutations are additional genetic factors that may be associated with a negative outcome despite the presence of activating mutations in the *EGFR* tyrosine kinase domain and should be screened in patients receiving TKIs if genomic means are to be used to guide therapy. Thirdly, most studies to date have ignored the functional impact of the CA tandem repeat polymorphism in intron 1 of the *EGFR* gene. A recent study by Sueoka-Aragane *et al.* showed that shorter CA repeats were associated with higher intrinsic levels of *EGFR* mRNA expression [2]. Furthermore, *EGFR* deletion at exon 19 was associated with shorter CA repeats in patients with elevated levels of *EGFR* mRNA. Further larger studies are certainly required to validate these findings.

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EGFR mutations in circulating lung cancer cells

Evaluation of: Maheswaran S, Sequist LV, Nagrath S *et al.*: Detection of mutations in *EGFR* in circulating lung cancer cells. *N. Engl. J. Med.* 359(4), 366–377 (2008).

Somatic *EGFR* mutations have some value as a predictive marker for response. Biopsy from lung cancer tissue is frequently small and difficult to obtain sequentially. Maheswaran *et al.*, in this small but elegant study, demonstrate the feasibility of characterizing circulating cancer cells using a microfluidic system [1].

Using only a small number of patients, they demonstrated that circulating tumor cells could be successfully isolated, and the *EGFR* mutations could be sequenced using standard bi-directional sequencing and allele specific sequencing. This method proved to be more sensitive in picking up mutations than from free circulating plasma DNA. They were able to detect the resistant T790M mutation and correlate that with a decreased progression-free survival despite initial response to *EGFR*

tyrosine kinase inhibitors. This mutation required additional amplification cycles before it became detectable suggesting that it was present in small number of cells. In addition they were able to quantitate an increase in abundance of the T790M allele as well the emergence of new activating mutations as disease progressed.

This study suggests that serial molecular analyzes of tumor from circulating cells is feasible. The other issue highlighted is that characterizing each individual mutation and the effect of treatment is important in order to successfully account for tumor heterogeneity. Other methods are also being evaluated with some success from free circulating DNA in serum [2] as well as from circulating tumor cells [3] using different methods of detection. These methods all have future implications on selecting and modifying treatment in patients. The overall applicability of such technology will need to be further evaluated in well-designed prospective clinical studies.

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