EDITORIAL

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Predictors of outcome for *EGFR*-mutant non-small-cell lung cancer treated with first-line tyrosine kinase inhibitors

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“...a deeper knowledge of the concurrent molecular environment supporting tumor development and progression may allow for further personalization of treatment and maximize the magnitude of benefit...”

The EGF receptor (EGFR) tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib, represent essential therapeutical weapons for the treatment of patients with advanced non-small-cell lung cancer (NSCLC). Their clinical efficacy has been clearly established following characterization of their appropriate molecular target, which has allowed us to retrospectively distinguish between responding versus nonresponding patients in the context of the preliminary development conducted in an ‘unselected’ population [1].

It has been widely demonstrated that the majority of objective responses to TKIs are retrospectively observed in patients harboring somatic mutations of the kinase domain of the *EGFR* gene, and that the presence of these mutations positively correlates with response to EGFR TKIs in prospective studies [1,2].

In this molecular context, the differential effect of TKIs according to various demographics, as well as other molecular factors (which may represent additional predictors of the efficacy of EGFR TKIs in patients with advanced NSCLC), deserves investigation.

Clinical & demographic factors

Female gender, nonsmoking status, adenocarcinoma histotype and Asian race have been initially identified as potential predictors for the efficacy of EGFR TKIs. However, after the discovery of the EGFR mutation as the main outcome predictor, these putative predictors became simply representative of a ‘clinically selected’ population with a high likelihood of harboring the sensitizing mutation. Data may be retrospectively extracted from the subgroup analyses of Phase III trials evaluating the efficacy of first-line EGFR TKIs, gefitinib and erlotinib, for advanced NSCLC patients.

In the context of the Iressa Pan-Asia Study (IPASS) [3], comparing gefitinib versus chemotherapy in previously untreated never-smoker or light ex-smoker patients with advanced adenocarcinoma (a ‘clinically selected’ population with an *EGFR* mutation rate of 60%), no difference in terms of overall survival (OS) was observed across all the analyzed clinical subgroups (sex, age, performance status [PS], smoking status and stage) [4]. Similar results were obtained in a similar ‘clinically

“...female gender, never-smoking status and exon 19 deletions were statistically significant predictors of a higher response rate for EGF receptor tyrosine kinase inhibitors...”

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selected' population in the context of the First-SIGNAL trial (Asian patients, never-smokers and advanced adenocarcinoma with a *EGFR* mutation rate of 44%) [5].

After the identification of *EGFR* mutations as the main determinants of the TKIs' clinical efficacy, two Phase III trials were conducted in 'molecularly selected' Asian patients affected by untreated *EGFR*-mutant metastatic NSCLC, to compare gefitinib versus chemotherapy [6,7]. In the NEJ002 study [6], the subgroup analyses showed that women had a longer progression-free survival (PFS) than men (6.5 vs 6.0 months; HR: 0.68; 95% CI: 0.51–0.92; $p = 0.01$). Conversely, in the WJTOG3405 trial, the PFS benefit was equally distributed among the different subgroups (sex, smoking status and mutation type) [7].

Concurrently, some clinical trials evaluated the efficacy of first-line erlotinib in 'unselected' or 'selected' NSCLC patients. The TORCH trial showed that first-line erlotinib followed at progression by chemotherapy was inferior to the standard reverse sequence in terms of OS for unselected patients with advanced NSCLC; no differences in OS were observed according to sex, histology, smoking status or *EGFR* mutation. A statistically significant interaction of treatment effect for patients treated with erlotinib followed by chemotherapy was observed according to sex ($p = 0.014$), smoking status ($p < 0.001$) and *EGFR* mutation ($p = 0.006$) in terms of PFS [8].

Two Phase III trials (one in Asian and the other in Caucasian populations) evaluated the efficacy of first-line erlotinib versus chemotherapy in advanced NSCLC carrying activating mutations of *EGFR* [9,10]. The OPTIMAL study, conducted in Asian patients, suggested that the PFS benefit obtained from erlotinib is extended in all clinical subgroups (regardless of age, sex, PS, disease stage, histology and smoking status) [9]. The EURTAC trial represents the first Phase III study that confirmed the efficacy of erlotinib versus standard chemotherapy affected by *EGFR*-mutant advanced NSCLC in European patients. The PFS benefit was observed across almost all of the subgroups, with the exception of former smokers: a significant interaction ($p = 0.0235$) was observed with regard to the benefit of erlotinib in PFS according to smoking status. At the multivariate analyses for PFS, only treatment group and PS were significant [10].

Although carried out using an indirect method, and therefore not constituting a

significant comparison, these latest studies suggest that the magnitude of the benefit obtained in the Asian population is substantially similar to that in the Caucasian population [10].

The LUX-Lung 3 is a randomized, Phase III trial evaluating the efficacy of afatinib (an irreversible *EGFR* blocker) versus chemotherapy for *EGFR*-mutant advanced NSCLC. The study population is mixed, constituting 72% Asian and 36% Caucasian patients. No significant interaction in PFS was observed according to demographic subgroups, even for ethnicity [11].

Molecular factors

Following the demonstration that NSCLCs carrying activating mutations of the *EGFR* gene are strongly dependent on *EGFR* signaling for their growth, the *EGFR* mutation has been universally recognized as the main predictive factor for TKIs' efficacy. Two major *EGFR* mutations have been identified (deletions in exon 19 and L858R mutation in exon 21), which account for almost 85% of *EGFR* mutations. These genetic alterations are associated with an impressive response to gefitinib, even if a possible alternative magnitude of benefit was suggested in patients harboring exon 19 deletions. Conversely, other genetic alterations, such as the T790M mutation and insertions in exon 20, are predictive of resistance to *EGFR* TKIs. Furthermore, in this largely unknown landscape of molecular alterations, an additional series of uncommon *EGFR* mutations (with a clinical relevance that has not yet been completely clarified) complicate the scenario [12].

The *EGFR* gene amplification represents another factor suspected to be potentially predictive of response to TKIs [13,14]. In the context of suspected predictors of resistance to *EGFR* TKIs, other molecular signaling pathways have been extensively studied, such as the *KRAS* mutation [15], as well as the *MET* amplification [16].

In the IPASS trial, PFS was significantly longer for gefitinib in patients with both exon 19 deletions (HR: 0.38; 95% CI: 0.26–0.56) and L858R mutations (HR: 0.55; 95% CI: 0.35–0.87), with a nonsignificant trend in favor of the exon 19 deletion group (HR: 0.78; 95% CI: 0.51–1.19). Conversely, overall response rate was significantly higher with gefitinib than with chemotherapy in the exon 19 deletion subgroup (84.8 vs 43.2%; OR: 7.23). The suggested potential predictive value of a high *EGFR* gene copy

number for PFS benefit in patients treated with gefitinib (treatment interaction test $p = 0.044$) seems likely to be driven by the coexistence of the *EGFR* mutation (77.6% of patients harbored both a high *EGFR* copy number and *EGFR*-mutant NSCLC; there was no observed benefit for those with an exclusively high gene copy number) [4].

In the context of the two Asian prospective trials (as well as in the IPASS study), no significant PFS difference for gefitinib was identified between the exon 19 deletions and the L858R mutation subgroups (11.5 vs 10.8 months; $p = 0.90$ in NEJ002; HR: 1.13, 95% CI: 0.63–2.03; $p = 0.681$) [6,7].

Although a consistent absence of differential effect according to mutation type was observed in trials exploring erlotinib for *EGFR*-mutant NSCLC, in the context of the EORTC study (similarly to the IPASS results), the benefit derived from erlotinib seemed to be greater (even if not statistically significant) for patients harboring the exon 19 deletions (HR: 0.30; 95% CI: 0.18–0.50; $p < 0.0001$) than for those with the L858R mutation (HR: 0.55; 95% CI: 0.29–1.02; $p = 0.0539$) [10].

This trend of benefit in favor of the exon 19 deletions compared with L858R mutation is also observed in the LUX-Lung 3 trial for patients treated with afatinib (HR: 0.28; 95% CI: 0.18–0.44 for exon 19 deletions and HR: 0.73; 95% CI: 0.46–1.17 for L858R mutations) [11].

The clinical relevance of uncommon *EGFR* mutations and their relative sensitivity/resistance to *EGFR* TKIs are still largely unknown. Wu *et al.* recently published a report of lung cancer patients harboring rare *EGFR* mutations: G719 and L861Q mutations are relatively frequent among the ‘uncommon’ mutations and are associated with a good response to TKIs (even

if lower than in presence of the classical *EGFR* mutations); only sporadic data are available for other very rare *EGFR* alterations [17].

In summary, in the context of the putative predictive role of clinical and demographic factors, conflicting evidences are available. More data seem to support the potential role of specific *EGFR* mutations as predictors of TKIs efficacy. A recent meta-analysis investigating the potential predictive role of three clinical/molecular factors in *EGFR*-mutant advanced NSCLC demonstrated that female gender, never-smoking status and exon 19 deletions were statistically significant predictors of a higher response rate for *EGFR* TKIs, and never-smokers also have a significantly longer PFS [18].

The retrospective nature of these data, extrapolated by the subgroup analyses of Phase III trials (thus clearly underpowered to detect differences and constituting a group of heterogeneous patients), does not leave room to speculate upon differential effects and simply serves to validate the essential predictive role of *EGFR*-activating mutations in advanced NSCLC treated with TKIs. Indeed, the potential predictive impact of a clinical/demographic characteristic, if any, appears to be strongly subordinate to the ‘power’ of that driving molecular alteration, which seems to exclusively sustain, as far as is currently known, the oncogenic process.

In this context, whereas the relative weight of a driver mutation impacts on the target therapy efficacy (and therefore on the patients outcome), a deeper knowledge of the concurrent molecular environment supporting tumor development and progression may allow for further personalization of treatment and maximize the magnitude of benefit deriving from the use of a specific target agent in a specific molecular subgroup of patients.

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