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Importance of patient selection for EGFR TKIs in lung cancer

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Abstract

Platinum-based chemotherapy has been the standard first-line treatment for patients with advanced non-small-cell lung cancer for decades. However, a recent study has shown the superiority of gefitinib treatment in comparison with chemotherapy in a molecularly selected cohort of patients harboring sensitizing *EGFR* mutations. These results demonstrate the importance of incorporating molecular selection into the design of lung cancer trials that use EGFR tyrosine kinase inhibitors.

In the past, the management of patients and the design of trials for advanced non-small-cell lung cancer (NSCLC) have been routinely based on the classification of tumors into categories based on histopathology and clinical stage at presentation. However, these classifications have remained largely unchanged for years and have reached their limit in providing critical information that might influence patient outcomes and treatment selection. This is evident by the very modest improvement in the survival of patients with lung cancer in the past few decades when treated with conventional chemotherapy.

Molecular-profiling studies indicate that activating mutations in genes such as *EGFR* and more recently *EML* and *ALK* translocations have a significant role in the development and progression of NSCLC, and presence of these mutations defines relatively small groups of patients who are sensitive to EGFR and ALK tyrosine kinase inhibitors (TKIs), respectively. Other mutations, such as those in *KRAS*, *TP53* and *STK11* genes are more frequent but at this time cannot be targeted effectively for treatment.¹

The selective use of targeted therapies based on molecular profiles from individual tumor samples seems to be a more rational approach to the management of lung cancer and holds the promise of improved patient outcomes. Indeed, the west Japan oncology Group (WJOG) 3405 trial by Mitsudomi *et al.*² is a great example of the potentials of such an approach. In this prospective, randomized trial, the EGFR TKI gefitinib was shown to be significantly superior to conventional chemotherapy for the first-line treatment of patients with advanced NSCLC harboring sensitizing *EGFR* mutations.

“Patients treated with gefitinib had a longer PFS than patients treated with cisplatin plus docetaxel...”

In this study, Mitsudomi *et al.*² compared gefitinib with cisplatin plus docetaxel in 172 chemotherapy-naïve patients who had stage IIIB/IV NSCLC harboring *EGFR* mutations

(either exon 19 deletions or L858R point mutations). This study was a randomized, open-label, phase III trial conducted in 36 centers in Japan. Initially, only patients with postoperative recurrence were eligible because it was expected that the mutation analysis was going to be easier to perform on resection material. However, because of the initial slow accrual, the protocol was amended to include patients with stage IIIB/ iv disease. In addition to the requirement of an *EGFR* mutation, patients were eligible if they were aged ≥ 75 years and had WHO performance status 0–1. Patients were randomly assigned to receive either gefitinib (250 mg/day), or docetaxel (60 mg/m²) and cisplatin (80 mg/m²) once every 21 days for three to six cycles. Treatment continued until progression of the disease, development of unacceptable toxic effects or completion of three to six chemotherapy cycles.

Overall, median progression-free survival (PFS) was 9.2 months (95% CI 8.0–13.9) in the gefitinib group and 6.3 months (95% CI 5.8–7.8) in the cisplatin plus docetaxel group (hazard ratio [HR] 0.489; 95% CI 0.336–0.710; $P < 0.0001$). Patients treated with gefitinib had a longer PFS than patients treated with cisplatin plus docetaxel in all subgroups analyzed including females, males, non-smokers, smokers, those with postoperative recurrence, stage IIIB/IV disease, exon 19 deletion and L858R point mutations. The objective response rate in the overall population with measurable disease was 62.1% in the gefitinib group and 32.2% in the cisplatin plus docetaxel group ($P < 0.0001$).

Prior to the WJOG trial, EGFR TKIs were initially tested as second-line therapy in unselected patient populations in which the frequency of *EGFR* mutations had been reported to be 12–15%. The BR21 trial³ showed the superiority of erlotinib in comparison with best supportive care, and the INTEREST trial⁴ showed that gefitinib had equivalent efficacy to second-line docetaxel in previously treated patients with advanced NSCLC. It was not until the subsequent discovery that mutations in the tyrosine kinase domain are associated with dramatic and sustained responses to EGFR TKIs that the potential of molecular selection was finally revealed.⁵

The initial clinical trials using EGFR TKIs as first-line therapies in NSCLC were conducted in unselected patient populations. A phase II study of erlotinib in chemotherapy-naïve patients with stage IIIB/IV NSCLC showed a response rate of just 22.7% and a median time-to-progression of 3 months.⁶ In addition, a pooled analysis of data from five first-line EGFR TKI trials in the advanced NSCLC setting showed that patients with 2 clinical predictors of response (Asian, female, non-smoker and adenocarcinoma histology) had a response rate of approximately 20% with a median time-to-progression of 4.4 months.⁷ Even with careful patient selection, the results in these earlier studies have not been as good as those reported in the WJOG trial.² The IPASS study was initiated to compare the efficacy of gefitinib versus carboplatin plus paclitaxel in the first-line treatment of clinically selected patients (East Asian, adenocarcinoma histology and no or minimal smoking history) with advanced NSCLC, in which the frequency of *EGFR* mutations in the patient population was approximately 60%.⁸ The objective response rate in the overall population was higher with gefitinib than with carboplatin plus paclitaxel (43.0% versus 32.2%, respectively; $P < 0.001$). However, there was no difference in median PFS (5.7 months versus 5.8 months, respectively) or overall survival (18.6 months versus 17.3 months respectively). By contrast,

a subset analysis showed that among patients with *EGFR* mutations, PFS was significantly longer in those receiving gefitinib compared with those receiving carboplatin plus paclitaxel (HR 0.48; 95% CI 0.36–0.64; $P<0.001$); the objective response rate was also greater in patients receiving gefitinib (71.2% versus 47.3%, respectively; $P<0.001$).

In contrast to other trials that have been conducted in unselected or clinically selected cohorts of patients (Table 1), the WJOG trial shows that gefitinib results in a better response rate and PFS compared with conventional chemotherapy in the first-line treatment of patients with advanced NSCLC harboring an activating *EGFR* mutation.

Furthermore, these findings correlate well with the results of the subset analysis of the IPAss trial and the North East Japan Gefitinib study Group 002 trial, in which a significant advantage in PFs was also reported for gefitinib versus chemotherapy in patients with *EGFR* sensitizing mutations (10.4 months versus 5.5 months, respectively; HR 0.357 95% CI 0.252–0.507, $P<0.05$).⁹ In conclusion, these results strongly suggest that genetic traits, and not the traditional clinical characteristics of patients, determine clinical efficacy. This knowledge should be translated into trial design and clinical practice, and the use of EGFR TKIs in NSCLC should be mainly limited to patients with *EGFR* mutations.

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Practice points

- Gefitinib is superior to chemotherapy in the first-line treatment of patients with advanced NSCLC harboring an activating *EGFR* mutation
- The use of EGFR TKIs in NSCLC should be mainly limited to patients with *EGFR* mutations

Table 1 |

TKIs versus chemotherapy as first-line therapy for NSCLC

Patient selection	EGFR TKIs			Platinum doublets		
	RR (%)	TTP or PFS (months)	OS(months)	RR (%)	TTP or PFS (months)	OS(months)
Unselected ^{6,7,10}	20–23	3–4.4	13.9–14.7	17–21	3.1–4.2	7.4–8.1
Clinically selected ^{*,8}	43–49	5.7–9.1	18.6–20.8	32	5.8	17.3
Molecularly selected ^{‡2,7–9}	62–71	9.2–13.1	28.0	32–47	5–6	23.6

^{*} East Asians, adenocarcinoma histology and no or former light smoking history

[‡]EGFR TKI sensitizing mutation-positive.

Abbreviations: OS, overall survival; PFS, progression-free survival; RR, response rate; TKI, tyrosine kinase inhibitor; TTP, time-to-progression.