Mirror Mirror on the Wall, Who Is the Fairest of Them All

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Clinical application of epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) as first-line treatment of advanced stage non–small-cell lung cancer with EGFR mutation is based on vigorous science.[1,2] Multiple randomized studies have independently confirmed gefitinib and erlotinib to be superior to platinum-based doublet chemotherapy.[3–6] Thus, it is natural to ask if gefitinib is better than erlotinib or vice versa. Lim et al.[7] addressed this question with a relatively large case-control study of 121 matched pairs of gefitinib-treated and erlotinib-treated patients. The pair-matching was appropriately based on gender, smoking history, performance status, and type of EGFR mutations. Authors reported similar tumor response rate (76.9% versus 74.4%, $p = 0.58$) and median progression-free survival (PFS) (11.7 versus 9.6 months; $p = 0.056$) between the gefitinib- and erlotinib-treated groups. Based on the data, Lim et al.[7] concluded equal effectiveness between the two EGFR TKIs. In short of a randomized comparative study, this report provides a relatively fair picture on the choice between gefitinib and erlotinib.

But how "fair" is this fair comparison? Limited by retrospective nature of this study, authors can only take on the required action of patient-pairing to assure similar characteristics between two groups. However, they have ignored one important factor, which is the number of prior treatment(s). As a result, there are significantly more patients receiving first-line gefitinib than patients with first-line erlotinib. Authors may argue that PFS on first-line EGFR TKI is not different from second-/third-line EGFR TKI.[8] Truth is that this remains assumptive. There are data suggesting that chemotherapy may have significant impact on EGFR mutation status.[9] Sequential intercalation of chemotherapy and EGFR TKI may also potentially improve PFS and overall survival of patients with EGFR mutations.[10] Authors have also taken the required action of performing contrasted computed tomography scan every 8 weeks for assessment of tumor status. But it is unclear how they have followed the progress of 83 patients (34% of the 242 enrolled patients) with bone metastasis, knowing well that computed tomography scan is not a reliable method of assessment for bone metastasis. Thus, their comparison is fairly fair but not convincingly fair.

We should also address the basic question of why we want to compare gefitinib with erlotinib? Both drugs are anilinoquinazolines with similar molecular structure (Figure 1) and both drug share similar mechanism of action in binding to EGFR ATP binding pocket. Pharmacokinetics of the two drugs is not dramatically different. Main difference between the two compounds is the maximum tolerated dose of erlotinib being estimated at 150 mg daily while maximum tolerated dose of gefitinib at 700 mg daily (which is much higher than the standard prescription dose).[11] A network meta-analysis of multiple phase II and III studies indicated potential longer PFS associated with erlotinib.[12] Value of this type of network meta-analysis is controversial, and yet the worthiness of engaging a large randomized study to confirm a relatively small difference in PFS between two similar drugs is arguable. Furthermore, it is common for doctors to continue EGFR TKI beyond disease progression (according to RECIST criteria).[13] PFS of erlotinib at OPTIMAL and EURTAC study was 13.1 and 9.2 months, respectively, and PFS of gefitinib at IPASS, NEJ002, and WJTOG3402 was 9.8, 10.8, and 9.2 months, respectively.[2–6] The numeric difference on PFS

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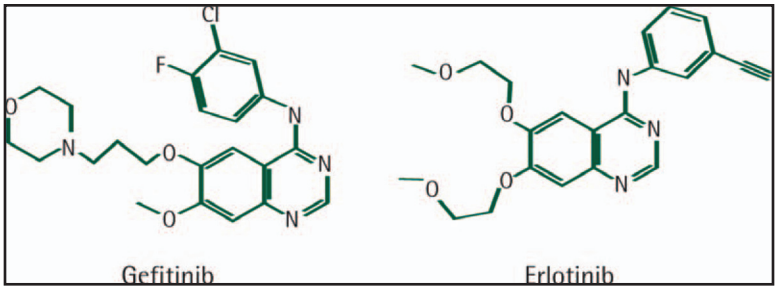

Figure 1. Molecular structure of gefitinib and erlotinib.

would have limited clinical implication if majority of patients continue with the same EGFR TKI beyond RECIST progression. In the absence of an objective, measurable, and clinically meaningful criteria for comparison, it will be almost impossible to define a better EGFR TKI. Only if we had a magic mirror, we might take on the subjective action of identifying the fairest of all EGFR TKIs.

REFERENCES

1. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350:2129–2139.
2. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–957.
3. Maemondo M, Inoue A, Kobayashi K, et al.; North-East Japan Study Group. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380–2388.
4. Mitsudomi T, Morita S, Yatabe Y, et al.; West Japan Oncology Group. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010;11:121–128.
5. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011;12:735–742.
6. Rosell R, Gervais R, Vergnenegre A, et al. Erlotinib versus chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor mutations: interim results of the European erlotinib versus chemotherapy (EURTAC) phase III randomized trial.
7. Lim SH, Lee JY, Sun JM, et al. Comparison of clinical outcomes following gefitinib and erlotinib treatment in non-small cell lung cancer patients harboring an epidermal growth factor receptor mutation in either exon 19 or 21. *J Thoracic Oncol* 2014;9:506–511.
8. Rosell R, Moran T, Queralt C, et al.; Spanish Lung Cancer Group. Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med* 2009;361:958–967.
9. Wang J, Chen K, Bai H, et al. Chemotherapy influence EGFR mutation status for Chinese patients with regionally advanced non-small cell lung cancer. *J Clin Oncol* 2011;29(suppl):abstr 7031.
10. Wu YL, Lee JS, Thongprasert S, et al. Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial. *Lancet Oncol* 2013;14:777–786.
11. Wolf M, Swaisland H, Averbuch S. Development of the novel biologically targeted anticancer agent gefitinib: determining the optimum dose for clinical efficacy. *Clin Cancer Res* 2004;10:4607–4613.
12. Paz-Ares L, Soulières D, Melezínek I, et al. Clinical outcomes in non-small-cell lung cancer patients with EGFR mutations: pooled analysis. *J Cell Mol Med* 2010;14:51–69.
13. Nishie K, Kawaguchi T, Tamiya A, et al. Epidermal growth factor receptor tyrosine kinase inhibitors beyond progressive disease: a retrospective analysis for Japanese patients with activating EGFR mutations. *J Thorac Oncol* 2012;7:1722–1727.