**EDITORIAL**

# The place of TKI in the treatment of EGFR mutation-positive lung cancer

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About half of all Asian patients with non-small cell lung cancer (NSCLC) have tumors that are positive for epidermal growth factor receptor (EGFR) mutation, for which tyrosine kinase inhibitors (TKI) such as gefitinib or erlotinib are effective. Gefitinib has been shown to be a useful second-line treatment for NSCLC after platinum-based chemotherapy [1], and some small-scale studies have also examined its activity as a first-line treatment for NSCLC, demonstrating a response rate of about 20% [2, 3], which is similar to that of other anticancer drugs for NSCLC. However, gefitinib has failed to exert any additional effect when combined with platinum-based chemotherapy as a first-line treatment for NSCLC [4, 5]. On the other hand, two biological studies have demonstrated that gefitinib is effective in specifically targeting the EGFR gene with deletion in exon 19 or point mutation in exon 21, and tumor regression induced by gefitinib in NSCLC patients has been shown to be correlated with the presence of these mutations in lung tumors [6, 7]. A Japanese study has demonstrated that patients with postoperative recurrence of EGFR mutation-positive NSCLC showed a good tumor response to gefitinib and achieved longer survival than patients whose tumors lacked EGFR mutation [8]. A study designed to compare carboplatin plus paclitaxel with gefitinib for chemo-naïve Asian patients with both EGFR mutation-positive and -negative NSCLC demonstrated that patients with EGFR mutation-positive tumors achieved significantly longer overall and progression-free survival with gefitinib than with carboplatin plus paclitaxel in subset analysis [9]. Thereafter, two large studies designed to compare platinum-based chemotherapy with gefitinib therapy for chemo-naïve NSCLC patients with EGFR mutation were performed in Japan. In both studies, the progression-free survival achieved with gefitinib was about twice as long as that achieved with standard platinum-based chemotherapy [10, 11]. These data indicated that gefitinib is an effective first-line chemotherapy for NSCLC harboring EGFR mutation.

Another EGFR TKI inhibitor, erlotinib, has also shown high activity in patients with EGFR mutation-positive tumors. A large-scale study of screening and treatment for patients with EGFR mutation-positive lung cancer demonstrated similar survival rates for first-line and second-line treatments using erlotinib [12]. The results indicated that EGFR TKI inhibitors did not induce cross-resistance to anti-cancer drugs such as platinum-based chemotherapeutic agents used for first-line chemotherapy, and that TKI inhibitors exhibited good efficacy irrespective of whether they were used for first- or second-line chemotherapy. Two studies designed to compare the activity of gefitinib with that of platinum-based chemotherapy in Japan demonstrated significantly better progression-free survival in the gefitinib treatment group. All of the patients in both studies were eligible for crossover treatment with platinum-based chemotherapy and gefitinib. Most patients who had received platinum-based first-line chemotherapy chose gefitinib for the second-line treatment, and achieved tumor regression with the latter agent. Thus, both studies demonstrated similar overall survival in the two

treatment groups [10, 11]. The results of the above studies indicated that patients with NSCLC harboring EGFR gene mutation were able to receive TKI inhibitors as either first-line or second-line treatments.

Which is considered the key drug for EGFR mutation-positive NSCLC? We prospectively examined the clinical benefits of treatments chosen on the basis of EGFR gene status [13]. Patients with EGFR mutation-positive tumors chose gefitinib as a second-line treatment after first-line platinum-based chemotherapy had failed, and achieved a tumor regression effect. Some of these responders benefited from platinum-based treatment, but others did not. Comparison of overall survival between responders and non-responders to first-line platinum-based chemotherapy demonstrated significantly longer survival of those who responded to second-line gefitinib treatment. If the primary endpoint of treatment for unresectable advanced NCSLC is prolongation of overall survival, every patient should be entitled to receive every potentially beneficial treatment. Except for severe pulmonary or skin toxicities, the adverse effects of EGFR TKI are mild, and most patients with NSCLC are able to tolerate it more easily than other anti-cancer drugs with moderate to severe toxicities. An appreciable proportion of patients reject chemotherapy because of its intolerable side effects. A comparative study found that about half of all patients who received first-line gefitinib treatment opted to continue with it, even if they developed resistance to the agent, rather than switching to other forms of chemotherapy such as platinum-based drugs for second-line treatment [10]. Thus, these patients were unable to receive the full benefit of chemotherapy, and accordingly had shorter survival times. Therefore we believe that the key treatment for patients with EGFR mutation-positive tumors is first-line standard platinum-based chemotherapy.

**Table 1.** Risk factors to select gefitinib treatment

| | No. of patients |
|---|---|
| Elderly | 9 |
| PS 2 to 4 | 7 |
| Rapid progression | 4 |
| Weight loss ≥10% | 3 |
| Multiple bone metastasis | 3 |
| Renal failure | 1 |
| Cerebral infarction | 1 |
| Poor pulmonary function | 1 |
| Patient refusal | 2 |

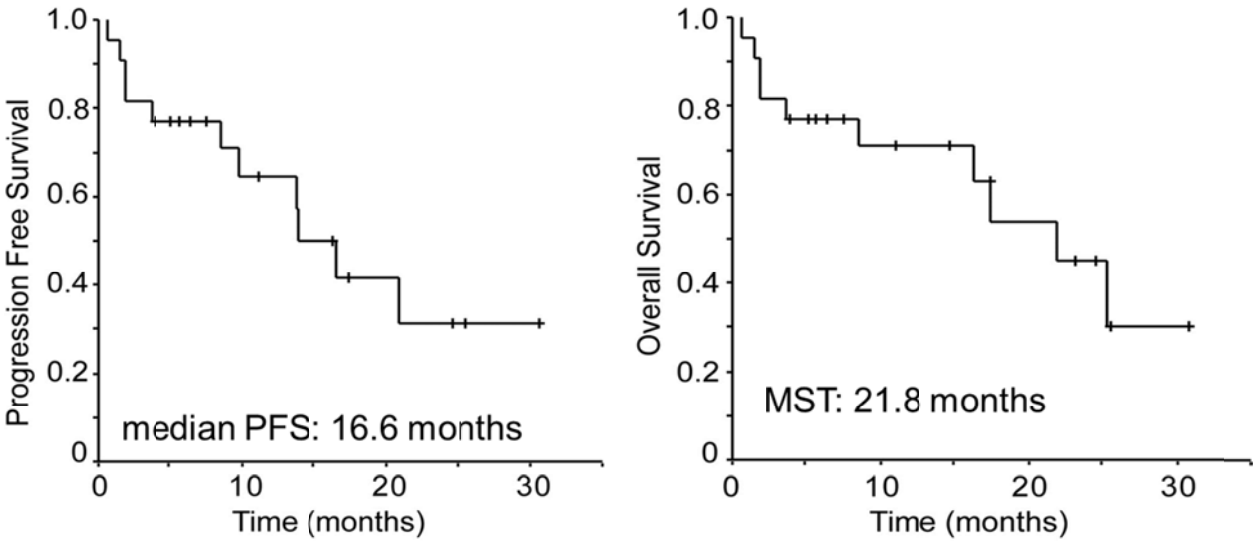


**Figure 1.** Examination of the efficacy of gefitinib


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High-risk patients for whom full-dose first-line platinum-based chemotherapy is not indicated might choose TKI as a first-line treatment. We retrospectively analyzed the backgrounds and outcomes of 23 patients with EGFR-mutated NSCLC who were treated with gefitinib between 2006 and 2009. Six patients were male and 17 were female, with a median age of 74 years (range 57-86 years). Sixteen patients had a PS of 1, 4 had a PS of 2, and 3 had a PS of 3 or 4. The reasons for choosing TKI were poor PS, elderly status, and the presence of underlying conditions such as cerebral infarction, renal failure or chronic obstructive pulmonary disease, for which full-dose standard platinum-based chemotherapy was contraindicated (Table 1). Examination of the efficacy of gefitinib for these high-risk patients with EGFR-mutated NSCLC showed that 16 (72.7%) of them responded. Gefitinib also improved their PS and yielded progression-free and median survival times of 16.6 and 21.8 months, respectively (Figure 1). These data suggested that high-risk patients with EGFR mutation-positive NSCLC tumors are good candidates for first-line TKI chemotherapy. No comparative study has yet demonstrated that TKI should become a standard treatment for high-risk patients with EGFR-mutated NSCLC; however such a study would be difficult to schedule and conduct. However, TKI might become a standard form of first-line chemotherapy if some phase II studies are able to demonstrate positive data.

Which therapeutic strategy for EGFR-mutated NSCLC can be regarded as carrying the least risk? Platinum-based chemotherapy has been used as a standard treatment strategy, and then gefitinib has been employed as a second-line treatment if the first-line treatment has failed, or if resistance has developed. A large-scale study of screening and treatment for patients with EGFR mutation-positive lung cancer demonstrated that TKI could be used at any time, but that patients preferred to receive TKI in the early stage in the hope that it would prove effective [12]. If platinum-based chemotherapy carries only minimal risk, then it is considered essential for such patients. Therefore, a treatment strategy involving concurrent platinum-based chemotherapy and TKI is desirable. Although no studies have assessed the efficacy of such treatment for patients with NSCLC of unknown EGFR status [4, 5], it is now known to be effective against NSCLC harboring EGFR mutation. Another possible strategy is platinum-based chemotherapy followed by TKI maintenance therapy. TKI could be administered earlier, for example after 1 or 2 cycles, if the initial treatment failed to reduce the tumor, and could be changed to a more effective TKI before drug resistance develops. It is important to choose a treatment strategy that is acceptable for the majority of patients, and for this purpose, less toxic first-line platinum-based regimens might be selected. Moreover, most cases of EGFR mutation are detected in non-squamous cell carcinoma, and drugs that are more effective against that histologic type of cancer should be chosen. Pemetrexed is the first drug for which effects have been found to differ according to the histologic type [14], being more effective against non-squamous than against squamous cell carcinoma. Therefore it might show promise for treatment of NSCLC harboring EGFR mutation. We are currently planning a prospective phase II study of carboplatin plus pemetrexed followed by gefitinib maintenance therapy, carboplatin being considered more acceptable to patients than cisplatin in view of its less severe toxicities.

In summary, use of EGFR-TKI is permissible for first- or second-line chemotherapy in patients with EGFR mutation-positive NSCLC. In future, the indications for TKI in patients with NSCLC harboring EGFR mutation should be clarified, including use in a concurrent combination with first-line platinum-based chemotherapy, maintenance therapy following first-line platinum-based chemotherapy, or first-line use for patients at high risk.

# References

[1] Fukuoka M, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard JY, Nishiwaki Y, Vansteenkiste J, Kudoh S, Rischin D, Eek R, Horai T, Noda K, Takata I, Smit E, Averbuch S, Macleod A, Feyereislova A, Dong RP, Baselga J. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) J Clin Oncol. 2003; 21: 2237-2246. PMid:12748244 http://dx.doi.org/10.1200/JCO.2003.10.038

[2] Niho S, Kubota K, Goto K, Yoh K, Ohmatsu H, Kakinuma R, Saijo N, Nishiwaki Y. First-line single agent treatment with gefitinib in patients with advanced non-small-cell lung cancer: a phase II study. J Clin Oncol. 2006; 24: 64-69. PMid:16382114 http://dx.doi.org/10.1200/JCO.2005.02.5825

[3] Inoue A, Suzuki T, Fukuhara T, Maemondo M, Kimura Y, Morikawa N, Watanabe H, Saijo Y, Nukiwa T. Prospective phase II study of gefitinib for chemotherapy-naive patients with advanced non-small-cell lung cancer with epidermal growth factor receptor gene mutations. J Clin Oncol. 2006; 24: 3340-3346. PMid:16785471 http://dx.doi.org/10.1200/JCO.2005.05.4692

[4] Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J, Haber DA. 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. PMid:15118073 http://dx.doi.org/10.1056/NEJMoa040938

[5] Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE, Meyerson M. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science. 2004; 304: 1497-1500. PMid:15118125 http://dx.doi.org/10.1126/science.1099314

[6] Giaccone G, Herbst RS, Manegold C, Scagliotti G, Rosell R, Miller V, Natale RB, Schiller JH, Von Pawel J, Pluzanska A, Gatzemeier U, Grous J, Ochs JS, Averbuch SD, Wolf MK, Rennie P, Fandi A, Johnson DH. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial – INTACT 1. J Clin Oncol. 2004; 22: 777-784. PMid:14990632 http://dx.doi.org/10.1200/JCO.2004.08.001

[7] Herbst RS, Giaccone G, Schiller JH, Natale RB, Miller V, Manegold C, Scagliotti G, Rosell R, Oliff I, Reeves JA, Wolf MK, Krebs AD, Averbuch SD, Ochs JS, Grous J, Fandi A, Johnson DH. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial – INTACT 2. J Clin Oncol. 2004; 22: 785-794. PMid:14990633 http://dx.doi.org/10.1200/JCO.2004.07.215

[8] Mitsudomi T, Kosaka T, Endoh H, Horio Y, Hida T, Mori S, Hatooka S, Shinoda M, Takahashi T, Yatabe Y. Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. J Clin Oncol. 2005; 23: 2513-2520. PMid:15738541 http://dx.doi.org/10.1200/JCO.2005.00.992

[9] Mok TS, Wu Y-L, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009; 361: 947-957. PMid:19692680 http://dx.doi.org/10.1056/NEJMoa0810699

[10] Maemondo M, Inoue, A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, Fujita Y, Okinaga S, Hirano H, Yoshimori K, Harada T, Ogura T, Ando M, Miyazawa H, Tanaka T, Saijo Y, Hagiwara K, Morita S, and Nukiwa T. for the 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. PMid:20573926 http://dx.doi.org/10.1056/NEJMoa0909530

[11] Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, Seto T, Satouchi M, Tada H, Hirashima T, Asami K, Katakami N, Takada M, Yoshioka H, Shibata K, Kudoh S, Shimizu E, Saito H, Toyooka S, Nakagawa K, Fukuoka M; 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. http://dx.doi.org/10.1016/S1470-2045(09)70364-X

[12] Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, Majem M, Lopez-Vivanco G, Isla D, Provencio M, Insa A, Massuti B, Gonzalez-Larriba JL, Paz-Ares L, Bover I, Garcia-Campelo R, Moreno MA, Catot S, Rolfo C, Reguart N, Palmero R, Sánchez JM, Bastus R, Mayo C, Bertran-Alamillo J, Molina MA, Sanchez JJ, Taron M; Spanish Lung Cancer Group. Screening for epidermal growth factor receptor mutations in lung cancer.N Engl J Med. 2009; 361: 958-967. PMid:19692684 http://dx.doi.org/10.1056/NEJMoa0904554

[13] Oshita F, Miyagi Y, Honda T, Murakami S, Kondo T, Saito H, Noda K, Yokose T, Kameda Y, Sakuma Y, Obata M and Yamada K. Prospective study of second-line chemotherapy for non-small cell lung cancer selected according to EGFR gene status. Journal of Experimental Therapeutics and Oncology. 2010; 8: 313-319. PMid:21222363

[14] Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, Serwatowski P, Gatzemeier U, Digumarti R, Zukin M, Lee JS, Mellemgaard A, Park K, Patil S, Rolski J, Goksel T, de Marinis F, Simms L, Sugarman KP, Gandara D Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008; 26: 3543-3551. PMid:18506025 http://dx.doi.org/10.1200/JCO.2007.15.0375