Gefitinib as monotherapy in the first-line setting in Non-small cell lung Cancer

R Gopall, C Hong, S Yi

Citation

R Gopall, C Hong, S Yi. *Gefitinib as monotherapy in the first-line setting in Non-small cell lung Cancer*. The Internet Journal of Pulmonary Medicine. 2008 Volume 11 Number 2.

Abstract

Recent advances in cancer therapy have resulted in the development ofdrugs that target mechanisms involved in neoplastic change and angiogenesis. Oneexample is Gefitinib ('Iressa', ZD1839), an orally-active epidermal growth factorreceptor tyrosine kinase inhibitor (EGFR-TKI) that blocks EGFR signaling,thereby inhibiting the growth, proliferation and survival of many solid tumors. This review discusses the potential of Gefitinib as monotherapy in the first line treatment of non-small cell lung cancer (NSCLC). Gefitinib showed promising results as a single agent in NSCLC in terms of tolerability profile and better disease response. Furthermore, it has been demonstrated that a molecularly defined population will benefit most from first-line treatment with Gefitinib.

INTRODUCTION

Over 1.35 million new cases of lung cancer are diagnosed every year worldwide and nearly 1.2 million people die as a result of this devastating disease - more than breast, colon and prostate cancer combined (1).

Lung cancer is classified as small-cell (13%) and non-small-cell (87%) and treatment differs based on the classification (1). Non-small cell lung cancer (NSCLC) is further divided into 3 subtypes based on histology: squamous-cell carcinoma, adenocarcinoma, and large-cell lung cancer. Although smoking is associated with all lung cancer types, its strongest association is with small-cell lung cancer and squamous-cell carcinoma. Adenocarcinoma is most frequently seen in non-smokers (2, 3).

As surgical techniques and combination treatment regimens have improved, the 1-year survival rate in lung cancer has increased slightly, from 35% in 1975-1979 to 41% in 2000-2003 (1). Nonetheless, the 5-year survival rate for all stages of lung cancer combined remains at only 15%. This is largely due to the fact that available screening tools are inadequate, and the vast majority of cases (84%) are diagnosed when the disease is no longer localized.(1) Although greater than 50% of patients with NSCLC are candidates for systemic treatment with chemotherapy, either for advanced disease or as adjuvant/neoadjuvant treatment in addition to local therapy, it has only shown modest activity in NSCLC (4).

The emergence of molecularly targeted agents such as those targeting the epidermal growth factor receptor (EGFR) represents a key treatment. Emerging data continue to elucidate their optimal use as well as the development of newer targeted agents. This review focuses on prospects of Oral Gefitinib ('Iressa', ZD1839) as a monotherapy in the first line treatment of NSCLC.

GEFITINIB (IRESSA)

Gefitinib is an EGFR-TKI (epidermal growth factor receptor-tyrosine kinase inhibitor), which targets and blocks the activity of the EGFR-TK, an enzyme that regulates intracellular signaling pathways implicated in cancer cell proliferation and survival. Growth factor signaling has been identified as a key driver of tumour growth and spread in a wide range of cancers (5).

Gefitinib (250 mg) is a once-daily oral therapy. It has a well-established, generally well-tolerated side-effect profile and is not typically associated with the cytotoxic side-effects commonly seen with chemotherapy. The most commonly seen side-effects of IRESSA are mild to moderate rash and diarrhea (6,7).

GEFITINIB IN THE FIRST-LINE SETTING

Platinum-based doublet chemotherapy is the standard of care for the first-line treatment of patients with metastatic NSCLC and good performance status (8). Among patients who are not candidates for platinum-based therapy due to

age or performance status, the use of sequential single agents is an option (9). With conventional chemotherapy regimens, response rates (RRs) remain at 20% to 40% and median survival is typically 8 to 10 months. Attempts to improve efficacy by adding cytotoxic agents to the standard platinum-based doublet regimen have resulted in increased toxicity without improved survival (10). This has led to increased interest in the use of molecularly targeted agents in the first-line setting.

Various trials with gefitinib as a first line treatment:

Gefitinib showed promising results as a single agent in refractory NSCLC in 2 phase 2 studies known as IDEAL (Iressa Dose Evaluation in Advanced Lung cancer) 1 and 2. In IDEAL 1, 210 pretreated patients were randomized to receive gefitinib at 250 or 500 mg/day (6). The overall response rate (ORR)- tumour shrinkage was 18.4% and 19% and overall survival (OS) was 7.6 months and 8.0 months for the lower dose and the higher dose groups, respectively. In IDEAL 2, 216 patients who had relapsed after platinum and docetaxel regimens were randomized to receive gefitinib 250 or 500 mg/day (7). Efficacy results were similar between the dosing groups; the ORR was 12% and the 1-year survival rate was 25%. In both studies, grade 3-4 adverse events (AEs) such as acneiform rash and diarrhea were more frequent with the higher dose (6,7).

A phase 2 study evaluated gefitinib 250 mg daily in 42 chemotherapy-naive patients with advanced NSCLC (11). Gefitinib showed some activity with an ORR of 30%, but the investigators observed an unacceptably high rate of grade 5 interstitial lung disease (4 patients). Another phase 2 study conducted in 37 patients with advanced NSCLC who were never-smokers evaluated the same dose of gefitinib, finding a 69% partial response (PR) rate and an 11% standard deviation (SD) rate. The estimated 1-year survival rate was 73% (12).

More recently, an open-label, randomized, parallel-group study called IPASS (Iressa Pan-ASia Study) evaluated gefitinib versus carboplatin/paclitaxel as first-line treatment in 1217 chemotherapy-naive patients in Asia whose tumors were of adenocarcinoma histology and who had either never smoked or were former light smokers (ceased smoking at least 15 years prior to study enrollment and had ≤ 10 pack-years exposure) (13). The study demonstrated that gefitinib had superior progression-free survival (PFS), that is, the lapse of time a person lives without his/her tumour progressing compared with carboplatin/paclitaxel in this population of clinically selected patients (25% with no progression after 1 year in the gefitinib arm versus 7% in the carboplatin/paclitaxel arm; hazard ratio (HR) 0.74; P<.0001).

Overall, treatment with gefitinib elicited a superior ORR (43% versus32%; P=.0001) and improvement in patient quality of life compared with chemotherapy (48% versus 41%; P=.0148 for Functional Assessment of Cancer Therapy - Lung [FACT-L] total score). Gefitinib had a more favorable tolerability profile and AEs (13).

Furthermore the IPASS trial showed that NSCLC patients with a mutation in the EGFR gene appear to be more likely to benefit from gefitinib (Iressa) than from conventional chemotherapy (14,15). Among patients with EGFR mutations, median progression-free survival was 9.5 months with gefitinib and 6.3 months with carboplatin/paclitaxel. Patients without EGFR mutations experienced a median progression free survival of 5.5 months with carboplatin/paclitaxel and 1.5 months with gefitinib (13). Hence EGFR mutation status was a strong predictive biomarker in this clinically selected first-line setting indicating that a molecularly defined population will benefit most from first-line Gefitinib (16,17).

Subsequently, the phase 3 INTEREST (Iressa Non-small-cell lung cancer Trial Evaluating REsponse and Survival against Taxotere) trial, conducted 1466 patients with NSCLC who had received 1 or 2 prior chemotherapy regimens, and found gefitinib to be non-inferior for survival (median OS of 7.6 months; 1-year survival of 32%) compared with docetaxel, and offered improved tolerability and patient quality of life (18). Preplanned subgroup analyses found one significant difference between the treatment groups: patients who had received 2 prior chemotherapy regimens had better survival with docetaxel than with gefitinib (P=.031). Overall, among patients taking gefitinib, 2.2% had grade 3/4 hematologic AEs, whereas docetaxel-treated patients had a 58.2% incidence of grade 3/4 neutropenia and a 42.3% incidence of grade 3/4 leucopenia (19,20).

In their recently published work the iTARGET trial (A phase II trial to assess the response to gefitinib in epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer tumors), Sequist and colleagues studied the use of gefitinib in chemotherapy-naive patients with identified EGFR mutations. 98 patients from 11 centres were prospectively screened for EGFR mutations and subsequently treated with

an EGFR TKI once such mutations were identified. 34 patients (35%) with EGFR mutations were identified (21). Three of the 98 samples (4%) were inadequate for EGFR testing. Of the 34 samples with EGFR mutations, the most common genomic changes were exon 19 deletions (18 patients, 53%) and the L858R point mutation of exon 21 (9 patients, 26%). Thirty-one of 34 patients were begun on gefitinib 250mg daily; one patient chose not to proceed with treatment, while 2 others were not started on gefitinib due to the presence of mutations associated with gefitinib resistance. With a median follow-up of 12.3 months, median PFS for the 31 treated patients was reported as 9.2 months (95% CI, 6.2-11.8 months), and median overall survival was 17.5 months (95% CI, 13.5-21.3 months) (21).

This trial is significant for several reasons. First, it demonstrates that prospective genetic testing prior to initiation of first-line therapy is feasible.

Second, the trial provides prospective confirmation of the results from prior studies in which mutation status was assessed. Namely, rates of response and disease control are high, and median times to progression and overall survival have been encouraging (16,17).

The trial also provides some additional evidence about the impact of some resistance mutations, such as T790M and MET amplification. Patients harboring these mutations in their pretreatment specimen tended to do poorly with gefitinib therapy, consistent with prior preclinical and clinical evidence (22,23).

CONCLUSION

Though it will be some time before final results from prospective, randomized trials comparing Gefitinib with conventional chemotherapy are available, we should consider the encouraging clinical outcomes of this targeted molecule as monotherapy in the first-line treatment in NSCLC. Overall, Gefitinib has a more favorable tolerability profile and better disease response. Moreover, mutation status is a strong predictive biomarker in determining that a molecularly defined population will benefit most from this drug.

Important avenues of current and future research in NSCLC include strategies to target mechanisms of treatment resistance including T790 mutations and MET amplification.

References

1. American Cancer Society. Cancer Facts and Figures 2008. Available at: http://www.cancer.org/downloads/STT/2008CAFFfinalsecured.pdf Accessed September 26, 2008.
2. Sato M, Shames DS, Gazdar AF, Minna JD. A translational view of the molecular pathogenesis of lung cancer. J Thorac Oncol. 2007; 2:327-343.
3. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers -- a different disease. Nat Rev Cancer. 2007; 7:778-790.
4. Giaccone G, Rodriguez JA. EGFR inhibitors: what have we learned from the treatment of lung cancer? Nature Clin Pract. 2005;2:557-5
5. Dassonville O, Bozec A, Fischel JL, Milano G. EGFR targeting therapies: monoclonal antibodies versus tyrosine kinase inhibitors. Similarities and differences. Crit Rev Oncol Hematol. 2007; 62:53-61.
6. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced nonsmall-cell lung cancer (The IDEAL 1 Trial) [corrected]. J Clin Oncol. 2003; 21:2237-2246.
7. Kris MG, Natale RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer. JAMA. 2003; 290:2149-2158.
8. Fong T, Morgensztern G, Govindan R. EGFR inhibitors as first-line therapy in advanced non-small cell lung cancer. J Thorac Oncol. 2008; 3:303-310.
9. Grossi F, Aita M, Follador A, et al. Sequential, alternating, and maintenance/consolidation therapy in advanced non-small cell lung cancer. Oncologist. 2007; 12:451-464.
10. Vansteenkiste J. Improving patient management in metastatic non-small cell lung cancer. Lung Cancer. 2007; 57(suppl 2):S12-S17.
11. Niho S, Kubota K, Goto K, et al. 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.
12. Lee DH, Han JY, Lee HG, et al. Gefitinib as a first-line therapy of advanced or metastatic adenocarcinoma of the lung in never-smokers. Clin Cancer Res. 2005;11:3032-3037.
13. Mok T. Phase III, randomised, open-label, first-line study of gefitinib vs carboplatin/paclitaxel (C/P) in clinically selected patients with advanced non-small-cell lung cancer (NSCLC). Program and abstracts of the 2008 Annual Meeting of the European Society of Medical Oncology; September 12-16, 2008; Stockholm, Sweden.
14. 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.
15. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci U S A. 2004; 101:13306-13311.
16. Asahina H, Yamazaki K, Kinoshita I, Sukoh N, Harada M, Yokouchi H, Ishida T, Ogura S, Kojima T, Okamoto Y, Fujita Y, Dosaka-Akita H, Isobe H, Nishimura M (2006) A phase II trial of gefitinib as first-line therapy for advanced non-small cell lung cancer with epidermal growth factor receptor mutations. Br J Cancer 95(8):998–1004.
17. Han SW, Kim TY, Hwang PG, Jeong S, Kim J, Choi IS,

et al. Predictive and prognostic impact of epidermal growth factor receptor mutation in non-small cell lung cancer patients treated with gefitinib. J Clin Oncol 2005; 23(11):2493–501.
18. Douillard J-Y, Kim E, Hirsch V, et al. Gefitinib (IRESSA) versus docetaxel in patients with locally advanced or metastatic non-small-cell lung cancer pre-treated with platinum-based chemotherapy: a randomized, open-label phase III study (INTEREST). J Thorac Oncol. 2007;2(8 suppl 4):S305.
19. Thatcher N, Chang A, Parikh P, Rodrigues PJ, Ciuleanu T, von Pawel J, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomized placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 2005; 366:1527–37.
20. Forsythe B, Faulkner K. Overview of the tolerability of gefitinib (IRESSATM) monotherapy. Clinical experience in non-small cell lung cancer. Drug Saf 2004; 27:1081–92.
21. Sequist LV, Martins RG, Spigel D, et al. First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic EGFR mutations. J Clin Oncol. 2008;26:2442-2449.
22. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET ampli- fication leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science. 2007;316:1039-1043.
23. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in PLoS Med. 2005;2:e73.

Author Information

Roshnee Gopall, MD
Department of Pulmonology, The first Affiliated Hospital of Chongqing Medical University

Chen Hong, MD
Associate Professor, Department of Pulmonology, The first Affiliated Hospital of Chongqing Medical University

Su Yi, MD
Associate Professor, Department of Pulmonology, The first Affiliated Hospital of Chongqing Medical University