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Long-term remission after erlotinib therapy in an elderly patient with advanced non-small cell lung cancer. Case report and conclusions for clinical practice

Abstract

Small molecule tyrosine kinase inhibitors (TKIs) of epidermal growth factor receptor (EGFR) — gefitinib and erlotinib — have recently been used as a therapeutic option in advanced non-small cell lung cancer (NSCLC) patients relapsing after first- or second-line chemotherapy. We report here a case of long-term remission in an elderly, non-smoking woman with advanced NSCLC after chemotherapy failure, who was selected for erlotinib therapy using demographic and clinical criteria. Based on this example and on the literature data we discuss the need for careful patient selection for this new therapeutic method.

Key words: non-small cell lung cancer, erlotinib, targeted therapies

Pol. Pneumonol. Allergol. 2008; 76: 451–455

Introduction

Small molecule tyrosine kinase inhibitors (TKIs) of epidermal growth factor receptor (EGFR) constitute a new class of molecularly targeted agents. Two of these compounds, erlotinib and gefitinib, have found their application in advanced non-small cell lung cancer (NSCLC).

In a phase III randomized study including patients relapsing after first- or second-line chemotherapy, erlotinib was demonstrated to increase median survival by 2 months compared to placebo [1]. Based on this study, erlotinib has been registered in several countries including Poland (gefitinib is registered almost exclusively in some Asian countries). The clinical efficacy of erlotinib is closely related to selected clinical and demographic factors (female sex, non-smokers, adenocarcinoma and Asian race) [2]. However, the strongest predictor of response to TKIs is alterations of *EGFR* gene [2–5]. In Poland patient selection to erlotinib treatment typically does not take into account these criteria and in particular no molecular testing is performed. We report here a case of long-term remission in an elderly, non smoking woman with advanced NSCLC after chemotherapy failure. She was selected for erlotinib therapy based on demographic and clinical criteria, and was subsequently found to have an *EGFR* gene mutation in her tumour. Based on this example and on the literature data we discuss the need for careful patient selection for this new therapeutic method.

Case report

In May 2002, chest radiography in a 78-year-old woman showed focal lesions in the middle lobe of the right lung. Diagnostic thoracotomy revealed

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Received: 10.03.2008

ISSN 0867–7077

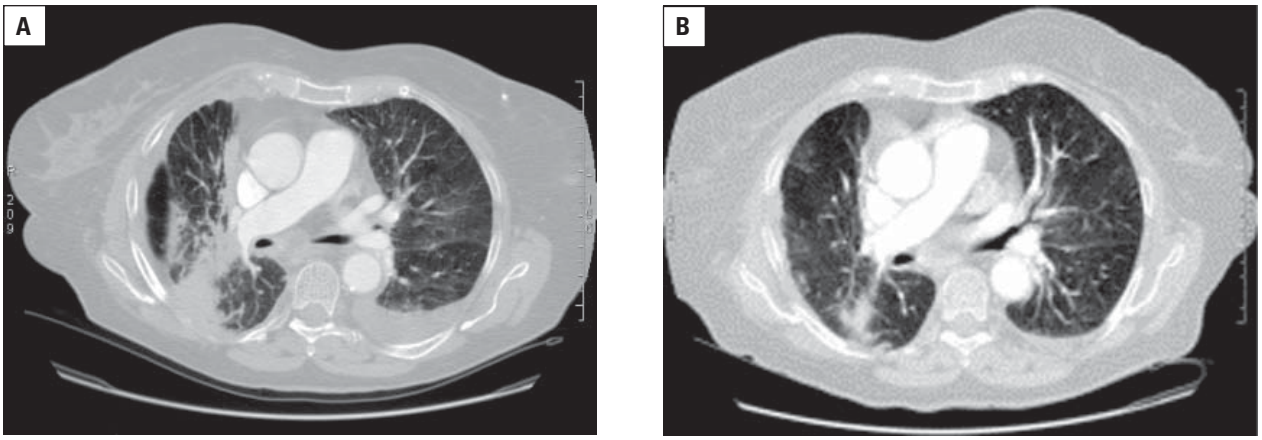

Figure 1. Chest CT examination. **A.** Prior to erlotinib treatment: Solid focal lesion sized 48 × 45 mm in the upper field of the right lung connected by a triangular shadow with the right hilum. A tumour of 13 mm in the lower field of the right lung adjacent to the atelectatic or fibrous strands. In the left pleural cavity a 30 mm layer of fluid. Mediastinal and hilar lymph nodes up to 11 mm. **B.** After 2 months of erlotinib treatment: Fibrous strands in the upper and middle fields of the right lung and fibrotic-atelectatic lesions in the base of the right lung — changes much smaller compared to previous examination. A trace of fluid in the left pleural cavity and thickening of the pleura. Mediastinal and hilar lymph nodes up to 10 mm

mixed type adenocarcinoma (papillary and non-mucinous bronchoalveolar type according to WHO 2004 classification) [6]. There was involvement of the parietal pleura, upper and lower lobes of the right lung, diaphragm and ipsilateral hilar lymph nodes (stage IV, pT4N1M1). The patient was a non-smoker, except for a short period during the Second World War. Based on the patient history and laboratory work-up, an accompanying degenerative joint disease, hypertension, stable coronary disease, secondary thrombocytosis and secondary hypothyroidism treated with levothyroxine were diagnosed. Treatment was started with pleurodesis using 60 mg of bleomycin. Owing to the patient's advanced age a monotherapy with iv vinorelbine at a dose of 25 mg/m^2 given on days 1 and 8 of a 21-day cycle was applied. She achieved partial remission after 3 cycles of chemotherapy administered between June and September 2002. Given the good treatment tolerance, cisplatin at a dose of 60 mg/m^2 on day 1 of each cycle was added to vinorelbine. Due to recurrent neutropaenia, asthenia and a loss of appetite, only 2 cycles of this regimen were given and chemotherapy was stopped in December 2002. Partial remission persisted until May 2006, when a chest computed tomography (CT) showed tumour progression in the mediastinal lymph nodes and in the right lung. At that time the patient complained of dyspnea, chest pain, cough and asthenia, and her WHO PS was 2. Due to advanced age and the reluctance of being exposed to another aggressive chemotherapy, an empirical treatment with oral etoposide at a dose of 100–150 mg on days 1–5 of a 28-day cycle was attempted. The treatment was poorly tolerated, the patient deteriorated with increased dyspnea, a lack of appetite and weight loss, and the chest tumour progressed (Fig. 1A); therefore, in July 2006 after 2 cycles, chemotherapy was stopped. Given the presence of clinical factors suggesting potential sensitivity to TKI therapy (non-smoking woman, adenocarcinoma with non-mucous bronchoalveolar component), oral erlotinib therapy at a single daily dose of 150 mg was attempted. An apparent clinical improvement (complete remission of cough and asthenia accompanied by increased appetite) was achieved after one month of erlotinib therapy. The chest CT performed after 2 months of treatment showed partial remission of the tumour (Fig. 1B). Apart from the mild facial acneiform rash, the treatment tolerance was good. The ex-post immunohistochemical examination of the primary tumour sample showed strong expression of EGFR, and denaturing high performance liquid chromatography (DHPLC) followed by DNA sequencing showed a p.E746_pA750 deletion in the exon 19 of the *EGFR* gene (Fig. 2A and 2B).

Partial tumour remission was also seen in the subsequent chest examinations performed within the next 15 months. Erlotinib therapy was continued until December 2007 and was then stopped due to deterioration of the patient's general status and progressing cardiopulmonary insufficiency. However, no apparent radiological evidence of tumour progression or TKI-related interstitial lung disease was found. Apart from the medicines the patient had already been prescribed (isosorbide mononitrate, trimetazidine, furosemide, ticlopidi-

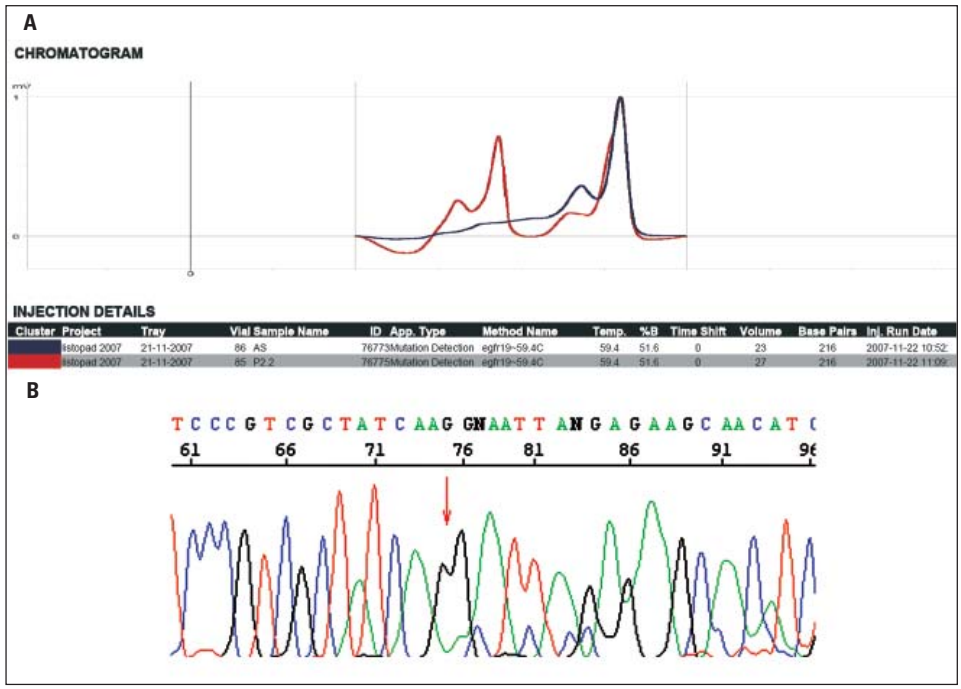

Figure 2. *EGFR* gene mutation. A. DHPLC chromatography. A difference seen in peaks between control sample (dark blue) and tumour sample (red). B. Sequencing image. Deletion seen in exon 19. Assays performed at the Department of Biology and Genetics, Medical University of Gdańsk, Poland, courtesy of Prof. J. Limon

ne hydrochloride and levothyroxine), corticosteroids, analgesics including morphine and (due to psychomotor agitation) midazolam maleinian infusion were applied. The patient died at the age of 83 years, a week after finishing erlotinib therapy. According to the family's will, no autopsy was performed.

Discussion

The optimal systemic second-line therapy of advanced NSCLC, particularly in elderly and in patients with bad performance status, has been a matter of controversy. In the presented case, due to contraindications to standard second-line chemotherapy with docetaxel or pemetrexed, an empirical oral etoposide treatment was applied, with no beneficial effect. Erlotinib also seems to be a valuable and well-tolerated therapeutic alternative to chemotherapy in elderly and fragile patients, and in those with brain metastases. Additionally, response with erlotinib is generally longer than with chemotherapy and is accompanied by an apparent clinical improvement. Another advantage of this therapy is an oral formulation, although its high cost is an issue. The most common side effects of TKIs include skin rash and diarrhoea which occur (usually in mild form) in 70% and 50% of patients, respectively. The most serious toxicity is interstitial lung disease, which in the registration studies was reported in < 1% of patients. The actual occurrence of this side effect may, however, be higher, as it may not manifest clinically and can only be diagnosed using specific testing, in particular diffusing capacity of the lung for carbon monoxide (DLCO). The risk of interstitial lung disease is higher in patients who have previously undergone chest radiotherapy or are concurrently applied some drugs including macrolides or proton pomp inhibitors. The efficacy of erlotinib in unselected advanced NSCLC patients is limited — in chemotherapy-pretreated Caucasians the objective response rate is in the range of 10% [7, 8]. Treatment selection to erlotinib therapy should therefore include known demographic and clinical factors related to increased response, such as female sex, adenocarcinoma (in particular non-mucinous bronchoalveolar type) and no previous tobacco exposure. The case presented here met all these criteria. In consequence, despite tumour advancement, old age and previous exposure to two lines of chemotherapy, a spectacular long-term objective remission accompanied by an apparent symptom relief was achieved.

The most important predictor of TKI treatment efficacy is molecular features of the tumour, in particular *EGFR* gene abnormalities [2–5]. The activating *EGFR* mutations (most commonly deletion

of the E746-A750 region in exon 19 and a *missense* mutation L858R in exon 21) are associated with a response rate in the range of 75–90% [9, 10]. Another feature strongly correlated with treatment response is the number of *EGFR* gene copies measured by fluorescence *in situ* hybridization (FISH) [2–4]. Retrospective subgroup analysis of phase III studies comparing gefitinib or erlotinib vs placebo showed significant prolongation of overall survival with TKIs in patients with amplification or high polysomy of *EGFR* gene, as opposed to those with normal *EGFR* status [2, 4]. The predictive value of EGFR expression by immunohistochemistry is limited. The lack of this feature is associated with low efficacy of TKIs; however, the expression is not predictive of this benefit [2]. A strong negative predictive factor for erlotinib therapy is mutation of the *K-ras* gene [11]; however, the occurrence of this abnormality in only 20–30% of tumours limits its clinical applicability. Although the predictive value of molecular assays has not yet been validated in prospective clinical trials, current knowledge justifies their use for patient selection to TKI therapy, as postulated in recent national recommendations for the use of systemic therapy in NSCLC [12]. Such selection may not only increase treatment efficacy but may also improve the pharmacoeconomic measures of this expensive therapy. The search for molecular assays allowing TKI therapy optimization in NSCLC continues. Until standard recommendations are developed, the pragmatic approach seems to be patient selection based on gene copy number determined by FISH. This method was found to predict most reliably the TKI treatment benefit, it is well known, and it has been successfully applied in other malignancies. Importantly, the molecular probes for this assay are commercially available. EGFR FISH testing should be performed in certified labs, for example in those already familiar with FISH testing for *HER2* in breast cancer.

Acknowledgements

The authors wish to thank Prof. Wojciech Kozłowski, the head of the Pathology Department at the Military Institute of Medicine in Warsaw and Prof. Janusz Limon, the head of the Department of Genetics and Biology at the Medical University of Gdańsk for their help in performing immunohistochemical and molecular assays.

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