Case Reports in Oncology

Case Rep Oncol 2013;6:189–196

DOI: 10.1159/000350680
Published online: March 29, 2013

1662–6575/13/0061–0189$38.00/0
www.karger.com/cro

Long-Term Treatment with Erlotinib for *EGFR* Wild-Type Non-Small Cell Lung Cancer: A Case Report

Genovefa Polychronidou Pavlos Papakotoulas

Theagenio Cancer Hospital, Thessaloniki, Greece

Key Words

Erlotinib · Gefitinib · Epidermal growth factor receptor · Tyrosine kinase inhibitors · Wild-type non-small cell lung cancer · Long-term maintenance treatment

Abstract

The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib are known to have greater efficacy in *EGFR* mutation-positive non-small cell lung cancer (NSCLC), although erlotinib also has activity in wild-type disease. We report the successful long-term maintenance treatment of a patient with *EGFR* wild-type NSCLC with gefitinib and later erlotinib. The patient (male; 44 years old; smoker) was diagnosed with *EGFR* wild-type NSCLC after computer tomography had revealed a mediastinal mass, and histology and mutation testing had identified the tumor as an *EGFR* wild-type grade 3 adenocarcinoma. The patient received multiple rounds of chemotherapy, followed by gefitinib maintenance (3 years). Later on, he received erlotinib maintenance and developed a persistent rash (grade 1/2) that lasted throughout the treatment. The patient's condition has remained stable on erlotinib for more than 5 years, with no evidence of progression. We describe the patient's disease course and treatment in the context of EGFR TKI therapy and the prognostic factors for long-term clinical outcomes of NSCLC, including the development of erlotinib-induced rash.

Introduction

With the introduction of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib, the approach to non-small cell lung cancer (NSCLC) treatment changed dramatically in the last decade. Clinical trials have demonstrated that erlotinib improves progression-free and overall survival in the second- and third-line

Dr. Genovefa Polychronidou
Theagenio Cancer Hospital
Al. Symeonidi 2
GR–54007 Thessaloniki (Greece)
E-Mail vefap@auth.gr

treatment of NSCLC [1] as well as in the maintenance setting [2], and it is approved for these indications [3]. Both erlotinib and gefitinib appear to be more efficacious in *EGFR* mutation-positive NSCLC (although erlotinib has also shown efficacy in *EGFR* wild-type disease). Erlotinib has demonstrated efficacy in the first-line treatment of *EGFR* mutation-positive NSCLC [4, 5] and is approved in this line of therapy [3]. Gefitinib is also indicated for the treatment of patients with locally advanced or metastatic NSCLC with *EGFR*-activating mutations [6]. Both agents target the tyrosine kinase domain of EGFR, inhibiting downstream signaling processes for growth and proliferation, and mutations in the *EGFR* gene can affect the behavior of the receptor and its response to inhibitors.

Most NSCLC clinical trials report survival outcomes over a couple of years, which is sufficient to identify significant differences in survival between treatment groups but also means that data on long-term treatment are limited. Here, we describe a case study of long-term erlotinib treatment of a patient with *EGFR* wild-type NSCLC.

Case Presentation

The patient was a Greek male aged 44 years, who presented to our hospital for diagnosis (December 2001). He was a smoker (40 cigarettes per day for 30 years), but stopped smoking in January 2008. Thorax X-ray for routine surgery demonstrated a suspicious lesion, and computer tomography (CT) revealed a mass in the posterior upper mediastinum with peripheral calcification and low densities. The mass was touching the aortic arch without putting pressure on it, and there were lesions in the upper lobes bilaterally. The patient underwent surgical excision of the mediastinal mass, and biopsies of the lung parenchyma lesions were taken. Histopathology showed a grade 3 lung adenocarcinoma. The CT scans of the abdomen and brain were normal (no metastases). The bone scans were controversial, with 'hot spots' in the sternum, twelfth thoracic vertebra, second lumbar vertebra and left sacroiliac joint. On diagnosis, the patient had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0. The biopsy sample of the primary tumor was negative for mutations in *EGFR* exons 18–21 by polymerase chain reaction.

The patient received carboplatin area under the curve (AUC) 5 (600 mg) plus epirubicin 70 mg/m^2 (130 mg) plus etoposide 100 mg/m^2 (200 mg) intravenously on day 1 and 300 mg orally on days 2 and 3. Six cycles were administered every 3 weeks (April–August 2002). No adverse events (AEs) were reported.

A CT scan of the thorax was carried out in August 2002, which revealed residual disease in the anterior mediastinum (2 cm in diameter) and metastatic lesions of the upper lobes (stable). Due to residual disease, clinical benefit and good PS, chemotherapy was continued. The patient received carboplatin AUC 5 (600 mg) plus gemcitabine 1,000 mg/m^2 (2,000 mg) on days 1 and 8, and four cycles were administered every 3 weeks (September–December 2002). No AEs were reported. The CT scan of the thorax was assessed as 'normal' (the lesion in the right upper lobe was assessed as calcified) (fig. 1a).

In November 2003, another CT scan of the thorax revealed three new lesions (one in the right middle lobe and two in the lateral basal part of the right lower lobe), indicating disease progression (fig. 1b). At this point, chemotherapy was resumed; the patient received carboplatin AUC 5 (600 mg) plus gemcitabine 1,000 mg/m^2 (2,000 mg) on days 1 and 8. Three cycles were administered every 3 weeks (December 2003–January 2004), and the response was stable disease. However, an allergic reaction to gemcitabine was noted and chemotherapy was therefore continued with docetaxel instead of gemcitabine. The patient

received carboplatin AUC 5 (450 mg) plus docetaxel 100 mg/m^2 (200 mg) every 3 weeks for six cycles (February–June 2004). No AEs were reported and the response was stable disease.

The patient started taking gefitinib in July 2004 and continued until August 2007 as part of the early access program of gefitinib. The disease remained stable and no AEs were observed. However, gefitinib administration had to be stopped because it was withdrawn by the Food and Drug Administration (FDA) for *EGFR* wild-type tumors and the expanded access program was discontinued. The patient was switched to erlotinib (August 2007) and treatment was continuing at the time of writing this case report in December 2012 (>5 years). He presented with grade 2 rash within 1 month of starting erlotinib. The rash (grade 1/2) lasted throughout the treatment, and grade 2 rash was treated with antibiotics (table 1). The disease remained stable during erlotinib maintenance; CT scans were carried out every 6 months and chest X-rays every 2 months. The patient has had no non-pleural metastases (fig. 1c).

Discussion

This case study describes the long-term maintenance treatment with erlotinib of a patient with *EGFR* wild-type NSCLC. In the first-line management of NSCLC, erlotinib is reserved for *EGFR* mutation-positive disease; however, erlotinib also has a role in the treatment of patients with *EGFR* wild-type disease in other lines of therapy (table 2) [6–11]. Erlotinib has shown improved clinical efficacy compared to chemotherapy in *EGFR* wild-type NSCLC in studies of maintenance and third-line therapy [7, 8]. Erlotinib and chemotherapy did not have significantly different second-line efficacy in patients with poor prognosis [10]. In line with these data, the European Society of Medical Oncology (ESMO) has recently published clinical guidelines on NSCLC treatment. The ESMO guidelines do not recommend that patients with *EGFR* wild-type NSCLC receive EGFR TKIs as first-line therapy as they are inferior to doublet chemotherapy in this patient group [12]. Maintenance and second-line therapy with EGFR TKIs are recommended for patients with *EGFR* mutation-positive status. However, the guidelines allow erlotinib treatment in patients with *EGFR* wild-type status who progress after first- or second-line chemotherapy if they have not previously received any EGFR TKIs [12]. In contrast, gefitinib has not demonstrated superiority to chemotherapy in *EGFR* wild-type disease [6] (table 2) and is not recommended or approved for the treatment of *EGFR* wild-type NSCLC.

EGFR TKI therapy is associated with the development of rash in many patients. In our patient, grade 2 rash developed after commencing erlotinib treatment. The rash persisted throughout the treatment period, but it was downgraded to grade 1 rash after 2 years. This is consistent with a report on side effects of long-term erlotinib, which described persistence of rash during erlotinib treatment over a few years [13]. Rash development has been correlated with EGFR TKI efficacy in NSCLC [14, 15]. In a meta-analysis [15] of 17 prospective trials and 7 retrospective case series, skin rash was an independent predictive factor for progression (HR 0.50, $p < 0.00001$) and survival (HR 0.30, $p < 0.0001$) in EGFR TKI-treated NSCLC patients. Patients who developed grade 2–4 rash were more likely to respond to the treatment (42%) compared to those who did not develop rash (7%). The authors of this meta-analysis suggest that skin rash may be a predictor for EGFR TKI efficacy, and this may reassure patients.

Other potentially favorable prognostic factors for long-term survival after NSCLC diagnosis have been investigated in the literature. Multivariate analyses of 26,957 patients with NSCLC identified good PS, never-smoker status, early-stage cancer, female gender, squamous

cell carcinoma histology and treatment as favorable prognostic factors [16]. A retrospective study [17] of 245 patients assessed factors associated with prolonged life expectancy; the use of maintenance therapy was a significant predictor for long-term survival, along with the absence of bone metastases and an ECOG PS of 0–1 at first progression, which correlates with aspects of the case reported here.

Long-term trials of erlotinib treatment are limited. However, a retrospective study [18] analyzed the profile of long-term NSCLC survivors (n = 301) to ascertain which patient subsets may benefit most from erlotinib treatment. Long-term erlotinib benefit was not only associated with good prognostic factors (e.g. ECOG PS 0–1), but also included patients with unfavorable risk factors such as male gender or smoking. Several long-term studies of gefitinib have been identified. One study of long-term survival (>5 years) in NSCLC (n = 124) showed that 8% of the patients survived for >5 years, and a good ECOG PS, adenocarcinoma histology and EGFR TKI therapy (gefitinib) played a role in long-term survival [19]. Another study [20] of long-term responders to gefitinib was carried out as part of the gefitinib expanded access program. Ten long-term responders out of 11 had adenocarcinomas, and long-term responders were more likely to have *EGFR* mutation-positive tumors, a lower number of metastatic sites and exclusively pulmonary or pleural metastasis compared intermediate responders or resistant patients. A case study of 3 refractory NSCLC patients [21] reported a >3-year survival with gefitinib treatment. The patients were female Japanese, and the tumor histology was adenocarcinoma. Finally, Reck and Gatzemeier [22] retrospectively analyzed the data from 240 patients treated with gefitinib, examining efficacy and tolerability of gefitinib in patients with long-term tumor control (defined as >6 months objective response or >9 months stable disease). Of the patients with long-term tumor control, 9 were female (mainly with adenocarcinoma) and 5 were male (mainly with bronchioloalveolar carcinoma). The patient described here had several prognostic factors for a good response (despite having *EGFR* wild-type disease), including adenocarcinoma histology, only pulmonary metastases and EGFR TKI maintenance treatment.

Conclusion

Our patient was diagnosed with *EGFR* wild-type NSCLC and treated with chemotherapy until the disease was stable. Maintenance therapy with gefitinib (3 years) was followed by erlotinib maintenance. The patient has now been treated with erlotinib for more than 5 years, with no progression of the disease.

Acknowledgements

The authors would like to thank the patient. Support for third-party writing assistance was provided by F. Hoffmann-La Roche Ltd.

Disclosure Statement

The authors declare that they have no conflicts of interest.

References

1 Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, van Kooten M, Dediu M, Findlay B, Tu D, Johnston D, Bezjak A, Clark G, Santabárbara P, Seymour L; National Cancer Institute of Canada Clinical Trials Group: Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123–132.

2 Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczésna A, Juhász E, Esteban E, Molinier O, Brugger W, Melezínek I, Klingelschmitt G, Klughammer B, Giaccone G; SATURN investigators: Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 2010;11:521–529.

3 Tarceva™ Summary of Product Characteristics, 2012. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000618/human_med_001077.jsp&mid=WC0b01ac058001d124 (accessed January 2013).

4 Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, Zhang S, Wang J, Zhou S, Ren S, Lu S, Zhang L, Hu C, Hu C, Luo Y, Chen L, Ye M, Huang J, Zhi X, Zhang Y, Xiu Q, Ma J, Zhang L, You C: 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.

5 Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, Garcia-Gomez R, Pallares C, Sanchez JM, Porta R, Cobo M, Garrido P, Longo F, Moran T, Insa A, De Marinis F, Corre R, Bover I, Illiano A, Dansin E, de Castro J, Milella M, Reguart N, Altavilla G, Jimenez U, Provencio M, Moreno MA, Terrasa J, Muñoz-Langa J, Valdivia J, Isla D, Domine M, Molinier O, Mazieres J, Baize N, Garcia-Campelo R, Robinet G, Rodriguez-Abreu D, Lopez-Vivanco G, Gebbia V, Ferrera-Delgado L, Bombaron P, Bernabe R, Bearz A, Artal A, Cortesi E, Rolfo C, Sanchez-Ronco M, Drozdowskyj A, Queralt C, de Aguirre I, Ramirez JL, Sanchez JJ, Molina MA, Taron M, Paz-Ares L; Spanish Lung Cancer Group in collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica: Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239–246.

6 Gefitinib™ Summary of Product Characteristics, 2012. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001016/human_med_000857.jsp&mid=WC0b01ac058001d125&murl=menus/medicines/medicines.jsp (accessed January 2013).

7 Zhu CQ, da Cunha Santos G, Ding K, Sakurada A, Cutz JC, Liu N, Zhang T, Marrano P, Whitehead M, Squire JA, Kamel-Reid S, Seymour L, Shepherd FA, Tsao MS; National Cancer Institute of Canada Clinical Trials Group Study BR.21: Role of K-RAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol 2008;26:4268–4275.

8 Brugger W, Triller N, Blasinska-Morawiec M, Curescu S, Sakalauskas R, Manikhas GM, Mazieres J, Whittom R, Ward C, Mayne K, Trunzer K, Cappuzzo F: Prospective molecular marker analyses of EGFR and K-RAS from a randomized, placebo-controlled study of erlotinib maintenance therapy in advanced non-small-cell lung cancer. J Clin Oncol 2011;29:4113–4120.

9 Kobayashi T, Koizumi T, Agatsuma T, Yasuo M, Tsushima K, Kubo K, Eda S, Kuraishi H, Koyama S, Hachiya T, Ohura N: A phase II trial of erlotinib in patients with EGFR wild-type advanced non-small-cell lung cancer. Cancer Chemother Pharmacol 2012;69:1241–1246.

10 Ciuleanu T, Stelmakh L, Cicenas S, Miliauskas S, Grigorescu AC, Hillenbach C, Johannsdottir HK, Klughammer B, Gonzalez EE: Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. Lancet Oncol 2012;13:300–308.

11 Martelli O, Garassino MC, Longo F, Moscetti L, Bettini A, Tomirotti M, Pavese I, Alabiso O, Sarobba G, Palmeri L, Bertolini A, Vattemi E, Ferrari V, Ardizzoia A, Mancuso A, Pellegrino A, Cavanna L, Contu A, Del Bene G, Labianca R, Fabbri MA, Bareggi C, Bonomi L, Veronese S, Lauricella C, Broggini M, Marabese M, Ganzinelli M, Rulli E, Copreni E, Floriani I, Marsoni S, Farina G, Scanni A: TAILOR: phase III trial comparing erlotinib versus docetaxel as second-line treatment of advanced non-small cell lung cancer (NSCLC) patients with wild type EGFR (wt) (abstract 4). J Exp Clin Oncol 2012;13:S2.

12 Peters S, Adjei AA, Gridelli C, Reck M, Kerr K, Felip E; ESMO Guidelines Working Group: Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23:vii56–vii64.

13 Becker A, van Wijk A, Smit EF, Postmus PE: Side-effects of long-term administration of erlotinib in patients with non-small cell lung cancer. J Thorac Oncol 2010;5:1477–1480.

14 Wacker B, Nagrani T, Weinberg J, Witt K, Clark G, Cagnoni PJ: Correlation between development of rash and efficacy in patients treated with the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib in two large phase III studies. Clin Cancer Res 2007;13:3913–3921.

15 Petrelli F, Borgonovo K, Cabiddu M, Lonati V, Barni S: Relationship between skin rash and outcome in non-small-cell lung cancer patients treated with anti-EGFR tyrosine kinase inhibitors: a literature-based meta-analysis of 24 trials. Lung Cancer 2012;78:8–15.

16 Kawaguchi T, Takada M, Kubo A, Matsumura A, Fukai S, Tamura A, Saito R, Maruyama Y, Kawahara M, Ignatius Ou SH: Performance status and smoking status are independent favorable prognostic factors for survival in non-small cell lung cancer: a comprehensive analysis of 26,957 patients with NSCLC. J Thorac Oncol 2010;5:620–630.
17 Giroux Leprieur E, Lavole A, Ruppert AM, Gounant V, Wislez M, Cadranel J, Milleron B: Factors associated with long-term survival of patients with advanced non-small cell lung cancer. Respirology 2012;17:134–142.
18 Schumann C, Heigener D, Dittrich I, Abenhardt W, Dederke B, Duell T, Matzdorff A, Raack BW, Steins M, Schneider CP: Long term benefit from erlotinib treatment is independent of prognostic factors and therapeutic response (abstract 9146). Eur J Cancer 2009;7:1.
19 Kaira K, Takahashi T, Murakami H, Tsuya A, Nakamura Y, Naito T, Endo M, Yamamoto N: Long-term survivors of more than 5 years in advanced non-small cell lung cancer. Lung Cancer 2010;67:120–123.
20 Gottschling S, Herpel E, Eberhardt WE, Heigener DF, Fischer JR, Köhne CH, Kortsik C, Kuhnt T, Muley T, Meister M, Bischoff HG, Klein P, Moldenhauer I, Schnabel PA, Thomas M, Penzel R: The gefitinib long-term responder (LTR) – a cancer stem-like cell story? Insights from molecular analyses of German long-term responders treated in the IRESSA expanded access program (EAP). Lung Cancer 2012;77:183–191.
21 Nakatomi K, Soda H, Kitazaki T, Nakano H, Uchida K, Urabe S, Nakamura Y, Hayashi T, Tsukamoto K, Kohno S: Long-term survival in three patients with metastatic non-small cell lung cancer treated with gefitinib. Lung Cancer 2006;52:253–255.
22 Reck M, Gatzemeier U: Benefit in lung function improvement and side-effect profile of long-term responders: an analysis of 14 NSCLC patients treated for at least 9 months with gefitinib. Lung Cancer 2005;50:107–114.

Table 1. Progression and treatment of erlotinib-associated rash in a patient (2007–2012)

	Rash	Treatment
August 2007	Patient started erlotinib (150 mg/day)	
October 2007	Grade 2 rash	Drug discontinuation for 1 week Clindamycin 300 mg 3 times daily (10 days)
December 2007	Grade 2 rash	Dose reduction of erlotinib to 100 mg Doxycycline 100 mg once daily (7 days)
March 2008	Grade 1 rash	No treatment
June 2008	Grade 2 rash	Doxycycline 100 mg once daily (7 days)
October 2008	Grade 2 rash	Doxycycline 100 mg once daily (14 days)
February 2009	Grade 2 rash	Doxycycline 100 mg once daily (14 days)
May 2009	Grade 2 rash	Doxycycline 100 mg once daily (14 days)
August 2009	Grade 1 rash	No treatment
November 2009	Grade 1 rash	No treatment
March 2010	Grade 1 rash	No treatment
June 2010	Grade 1 rash	No treatment
July 2010	Grade 1 rash	No treatment
August 2012	Grade 1 rash	No treatment

Table 2. Median progression-free survival and overall survival for erlotinib and gefitinib in wild-type disease [6–11]

Trial	Line of therapy		Patients n	Gefitinib	Erlotinib	Chemo-therapy	Placebo	HR (95% CI)	p value
BR.21 [7]	Second/third	OS	170	–	7.9 months	–	3.3 months	0.74 (0.52–1.05)	0.0924
SATURN [8]	Maintenance	PFS	388	–	12.0 weeks	–	8.9 weeks	0.78 (0.63–0.96)	0.0185
		OS		–	nr	–	nr	0.77 (0.61–0.97)	0.0243
Phase II [9]	Second	PFS	31	–	2.1 months	–	–	–	–
		OS		–	7.7 months	–	–	–	–
TITAN [10]	Second	PFS	149	–	nr	–	–	1·25 (0·88–1·78)	0.200
		OS		–	nr	–	–	0.85 (0.59–1.22)	0.37
TAILOR [11]	Second	PFS		–	2.4 months	2.8 months		0.69 (0.52–0.93)	0.014
ISEL [6]	Second/third	TTF	189	2.0 months	–	–	2.6 months	1.10 (0.78–1.56)	0.5771
		OS		3.7 months	–	–	5.9 months	1.16 (0.79–1.72)	0.4449
INTEREST [6]	Second	PFS	253	1.7 months	–	2.6 months	–	1.24 (0.94–1.64)	0.1353
		OS		10.4 months	–	12.2 months	–	1.04 (0.80–1.35)	0.7711
IPASS [6]	First	PFS	176	1.5 months	–	5.5 months	–	2.85 (2.05–3.98)	<0.0001
		OS		11.2 months	–	12.7 months	–	1.18 (0.86–14.6)	nr

OS = Overall survival; PFS = progression-free survival; – = not applicable; nr = not reported; TTF = time-to-treatment failure.

DOI: 10.1159/000350680

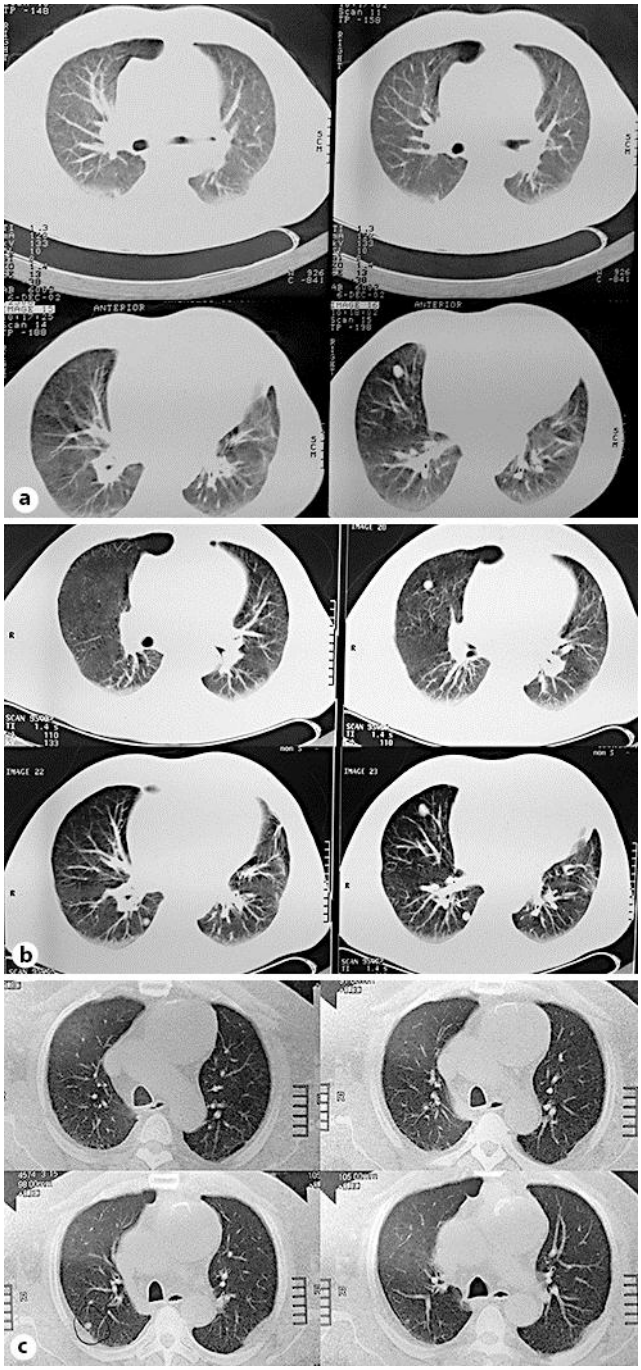

Fig. 1. CT scans of a long-term NSCLC survivor **a** after chemotherapy (CT of the thorax was assessed as 'normal' – the lesion in the right upper lobe was assessed as calcified), **b** during disease progression and **c** during stable disease after long-term treatment with erlotinib.