Case Report

Response of Leptomeningeal Metastases in EGFR-Mutated Non-Small-Cell Lung Cancer to Afatinib in the Absence of Radiotherapy

Néstor Llinás-Quintero,1 David González-Hoyos,2 Andrés Yepes,1 Diego A. Herrera,3 Sebastián Peláez-Arroyave,3 Carlos Caicedo-Zamudio,3 Erick Blanco-Daza,4 and Javier Cuello-López1

1Clinical Oncology Group, Fundación Colombiana de Cancerología-Clinica Vida, Medellín, Colombia
2School of Medicine, CES University, Medellín, Colombia
3Diagnostic Imaging Group, CEDIMED, Medellín, Colombia
4School of Medicine, UPB University, Medellín, Colombia

Correspondence should be addressed to Néstor Llinás-Quintero; nllinas71@gmail.com

Received 5 July 2019; Accepted 19 August 2019; Published 16 September 2019

Academic Editor: Francesco A. Mauri

Copyright © 2019 Néstor Llinás-Quintero et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Palliative radiotherapy is currently the medical standard of care for non-small-cell lung cancer (NSCLC) patients with symptomatic CNS and leptomeningeal disease. We report the case of a 62-year-old male patient with EGFR mutation (del19+) NSCLC with symptomatic lymph node, bone, CNS, and leptomeningeal metastases. Taking into account on one hand the response to tyrosine kinase inhibitors (TKIs) and on the other hand the short- to medium-term side effects of radiotherapy and the lack of timely availability in our healthcare system, the patient was treated with afatinib (40 mg daily) and exhibited a rapid response with improvement of neurological symptoms. The patient presented partial response of extracranial, CNS, and leptomeningeal lesions at 3, 6, and 12 months of treatment, currently completing 16 months of progression-free survival despite presenting mild dermatological and gastrointestinal toxicities. Afatinib is an effective and safe option in patients with NSCLC EGFR mutation del19+ with CNS and leptomeningeal compromise avoiding or delaying radiotherapy and its side effects, especially in countries where there is a lack of access to this kind of therapy.

1. Introduction

Lung cancer is the leading cause of cancer death worldwide [1, 2]. In these patients, central nervous system (CNS) metastases are estimated to occur in 30 to 50% of patients, which carries a poor prognosis of 4.7% in a 5-year relative survival rate, which is even poorer if there is symptomatic leptomeningeal disease [1–3].

Among EGFR-mutant NSCLC patients, leptomeningeal disease occurs in approximately 9% of cases, with a median overall survival of 3 months [4–8]. Thus, treatment goals are improved quality of life and prolonged survival. To date, studies providing evidence on how to best approach these patients are limited; nonetheless, currently used treatment regimens include radiotherapy, intrathecal chemotherapy, and systemic therapy, which—despite achieving various outcomes—carry a poor prognosis [5–7, 9–11].

Treatment of brain metastasis involves whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and surgery. However, with the improvement of systemic therapy, especially for treatment of tumors presenting anaplastic lymphoma kinase (ALK) translocations and epidermal growth factor receptor (EGFR) mutations, cancer control can be achieved. For instance, the third-generation
EGFR tyrosine kinase inhibitor (EGFR-TKI) osimertinib has been evaluated in prospective trials conducted in patients with brain metastases and showed significant improvement in progression-free-survival (PFS) compared to first-generation EGFR-TKI. However, the cost of treatment has limited the access to this therapy [3, 5, 6, 11–20]. Furthermore, in patients with advanced EGFR-mutant NSCLC, afatinib—a second-generation EGFR-TKI—has demonstrated activity against CNS and leptomeningeal metastases (LM) and to perform superiorly to gefitinib—a first-generation EGFR-TKI [21–24].

2. Case Description

A 62-year-old male with past medical history of hypertension, type 2 diabetes, and fibromyalgia presented to our clinic with complaints of back pain and dyspnea. The chest X-ray showed bilateral micronodular opacities and a nodule in the paramediastinal and aortic regions. Due to worsening of symptoms, a CT scan was performed, and a $35 \times 27 \times 33$ mm speculated mass in the right upper lobe, bilateral mediastinal lymphadenopathies, and bilateral apical diffuse reticulonodular and micronodular opacities were identified. On bronchoscopy, no endobronchial lesions were identified, with a high suspicion of malignancy in aspiration cytology. PET-CT was performed and showed bilateral diffuse pulmonary metastatic disease, lesions in most vertebrae (C2, C6, C7, T2, T4-T6, T8-T12, L1-L5, sacral segments S1 and S2, and both iliac spines), and mediastinal lymph node involvement. A videothoracoscopy-guided segmental lobectomy plus mediastinal lymphadenectomy was performed for pathology confirmation. The pathology report indicated moderately differentiated lung multifocal lepidic-predominant adenocarcinoma, with lymph node involvement and with visceral, pleural, lymphovascular, and border invasion.

The patient was referred to clinical oncology, as he continued presenting symptoms complaining of persistent cough, weight loss, headache, and dyspnea, presenting a NYHA functional class III/IV and poor performance status (Karnofsky Performance Status Scale 70%). Upon physical examination, bibasilar rales and a positive percussion test in the dorsal vertebrae were identified. Laboratory tests showed normal renal, hepatic, and hematologic function. The patient was diagnosed with stage IVB (T2N3M1c) NSCLC adenocarcinoma with bone, mediastinal lymph node, and contralateral lung involvement. A brain MRI showed multiple
nodular lesions in the brain and cerebellar parenchyma with leptomeningeal enhancement. A spinal MRI confirmed the metastatic involvement in the vertebrae, as indicated by the previous PET-CT scan, but without epidural infiltration. In addition, positive EGFR exon 19 deletion was also identified.

Due to the lack of timely access to radiotherapy, and considering its associated side effects, radiation therapy was postponed, and palliative care was initiated with treatment with a tyrosine kinase inhibitor, because of his EGFR mutational status. The patient was started on a 40 mg/day dose of afatinib treatment, administered orally, until there was evidence of disease progression or drug tolerance. Additionally, the patient received antiresorptive therapy with intravenous bisphosphonates every month to treat his bone metastasis. Immediately after initiating therapy, the patient exhibited rapid symptom and performance status improvement and was able to tolerate treatment; however, he presented grade 1 gastrointestinal toxicity and grade 2 dermatological toxicity. Follow-up images at 3, 6, and 12 months of treatment showed partial response of extracranial, CNS, and leptomeningeal lesions (Figures 1 and 2). To date, the patient has completed 16 months of treatment, displaying adequate tolerance and partial response to therapy, as well as a preserved quality of life and no evidence of disease progression.

### 3. Discussion

EGFR mutations are observed in 15% of lung cancer cases and have been associated with metastatic tropism to the brain, as well as to predict sensitivity to tyrosine kinase inhibitors (TKIs) [3, 5, 7, 8, 13, 25]. A retrospective study found a frequency of 7.8% of the lepidic subtypes with 68.8% of them with EGFR mutation [26]. In non-small-cell lung cancer, TKIs have proven efficacy in improvement of progression-free survival, response rate, and quality of life when compared to chemotherapy in patients with an EGFR mutation and are included in the current standard of care for patients with symptomatic brain metastasis together with WBRT [3–6, 13, 25–28].

The incidence of leptomeningeal carcinomatosis (LC) in EGFR-mutant NSCLC patients is 9%, and while median overall survival (OS) is 3-4.5 months, 44% have prolonged survival of more than 6 months. In a retrospective analysis of patients with LC by NSCLC with EGFR mutations, TKI therapy after LC diagnosis was an independent predictive factor of extended survival (median OS 10.0 vs. 3.3 months, HR = 0.218, p < 0.001), whereas poor Eastern Cooperative Oncology Group performance status (p < 0.001, HR = 3.657) was a predictor of poor survival [29, 30]. In that study, the active treatment with WBRT did not prolong OS for EGFR-mutated patients.
WBRT has been used as a therapeutic strategy in patients with brain and leptomeningeal metastases to relieve symptoms, to reduce bulky or nodular disease, and to correct CSF flow [31]. However, given its short and long-term adverse effects, and the increasing survival with the use of TKIs, even in patients with cerebral involvement, WBRT is being used less in patients with NSCLC with oncodriver gene mutations [6, 27]. Recently, Wang et al. published a meta-analysis that evaluated the role of WBRT as a treatment associated with TKIs in patients with NSCLC with brain metastases and EGFR mutation [10]. This meta-analysis included seven eligible studies for a total of 1086 patients. Compared to TKI alone, upfront WBRT plus TKI showed better PFS (HR = 0.72, 95% CI: 0.53-0.97, p = 0.028) and OS (HR = 0.70, 95% CI: 0.53-0.93, p = 0.015). Metagression analyses and subgroup analyses showed that while patients with a limited number of brain metastases (<3) benefited from WBRT as evidenced by improved OS (HR = 0.54, 95% CI: 0.41-0.72, p ≤ 0.001), patients with more than 3 brain metastases did not show OS benefit by undergoing WBRT [10].

Emerging evidence indicates that second- (afatinib) and third-generation (osimertinib) EGFR TKIs effectively penetrate the blood-brain barrier (BBB) and therefore represent viable treatment options for CNS lesions and can reduce the risk of CNS progression. These agents should be therefore considered as first-line treatment options in patients with EGFR mutation-positive NSCLC who have brain metastases and/or LM [7, 8, 32].

Evidence of the activity of afatinib against brain metastases has also been demonstrated by recent risk analyses of the LUX-Lung 3 and 6 studies [24]. In patients with a target brain lesion at the start of afatinib treatment, the risk of CNS progression (34%) was lower than the risk of non-CNS progression (48%). De novo CNS progression was observed in only 5% vs. 71% in non-CNS progression of patients after 24 months [13]. A combined analysis of the LUX-Lung 3 and LUX-Lung 6 trials showed benefit in PFS with afatinib as first-line treatment compared with chemotherapy in patients with asymptomatic CNS metastases (8.2 vs. 5.4 months; hazard ratio, 0.50; p = 0.0297) [24].

Osimertinib, a third-generation TKI that selectively inhibits both EGFR-TKI-sensitizing and EGFR T790M resistance mutations, has been approved as first-line treatment for EGFR mutation-positive NSCLC and as second-line after EGFR-TKI treatment in patients with EGFR T790M resistance mutations [16]. Osimertinib has a high bioavailability in the CNS [18]. In the FLAURA study, 556 patients with NSCLC and positive EGFR mutation were randomly assigned to osimertinib or standard of care (erlotinib or gefitinib). In this trial, there was a significantly longer PFS in the osimertinib group (18.9 versus 10.2 months; hazard ratio 0.46, 95% CI: 0.37-0.57) [18]. A subanalysis of the FLAURA study in patients with CNS involvement included 128 patients of the 200 that had available brain scans at the baseline. This subanalysis showed that median CNS progression-free survival was not reached with osimertinib (95% CI, 16.5 months to not calculable) and was 13.9 months with standard EGFR-TKIs (95% CI, 8.3 months to not calculable) (hazard ratio, 0.48; 95% CI: 0.26 to 0.86; p = 0.014) [19].

In our case, we were unable to provide treatment with osimertinib since it is not currently approved in our country; thus, despite evidence of brain and leptomeningeal metastases, the patient was started on treatment with afatinib, taking into account the evidence on clinical response of EGFR-mutated NSCLC without prior radiotherapy. This therapeutic strategy allowed postponing radiotherapy and its side effects. In addition, in some cases, access to radiotherapy can be difficult and delayed, putting the patient’s life at risk. The partial response to treatment with improvement of his performance status and an outstanding progression-free survival strongly supports the safety and effectiveness of this therapy. Afatinib is an effective and relatively safe option in patients with EGFR mutation del19+ with symptomatic CNS and leptomeningeal metastases, especially in countries where the access to radiotherapy is still limited. Additional studies should be conducted to obtain more information on the safety and efficacy of tyrosine kinase inhibitors, especially in patients with CNS and leptomeningeal metastatic involvement.

Conflicts of Interest

All authors have declared no conflicts of interest.

Acknowledgments

The authors would like to thank Fundación Colombiana de Cancerología-Clinica Vida.

References

[1] N. Howlader, A. Noone, and M. Krapcho, Surveillance, Epidemiology, and End Results (SEER) Program. SEER Cancer Statistics Review, 1975-2012 (updated August 20, 2015), National Cancer Institute, Bethesda, MD, USA, 2016, based on November 2014 SEER data submission, posted to the SEER web site, April 2015.

[2] O. Arrieta, C. Villarreal-Garza, J. Zamora et al., “Long-term survival in patients with non-small cell lung cancer and synchronous brain metastasis treated with whole-brain radiotherapy and thoracic chemoradiation,” Radiation Oncology, vol. 6, no. 1, p. 166, 2011.

[3] D. E. Dawe, J. N. Greenspoon, and P. M. Ellis, “Brain metastases in non–small-cell lung cancer,” Clinical Lung Cancer, vol. 15, no. 4, pp. 249–257, 2014.

[4] B. C. Liao, J. H. Lee, C. C. Lin et al., “Epidermal growth factor receptor tyrosine kinase inhibitors for non–small-cell lung cancer patients with leptomeningeal carcinomatosis,” Journal of Thoracic Oncology, vol. 10, no. 12, pp. 1754–1761, 2015.

[5] N. Choobak, S. Lefresne, S. C. Lau, and C. Ho, “CNS Metastases in epidermal growth factor receptor mutation–positive non–small-cell lung cancer: impact on health resource utilization,” Journal of Oncology Practice, vol. 14, no. 10, pp. e612–e620, 2018.

[6] W. J. Kelly, N. J. Shah, and D. S. Subramaniam, “Management of brain metastases in epidermal growth factor receptor mutant non-small-cell lung cancer,” Frontiers in Oncology, vol. 8, p. 208, 2018.

[7] J. Remon, E. Le Rhun, and B. Besse, “Leptomeningeal carcinomatosis in non-small cell lung cancer patients: a continuing
challenge in the personalized treatment era,” Cancer Treatment Reviews, vol. 53, pp. 128–137, 2017.

[8] J. Remon and B. Besse, “Brain metastases in oncogene-addicted non-small cell lung cancer patients: incidence and treatment,” Frontiers in Oncology, vol. 8, p. 88, 2018.

[9] J. W. Hyun, I. H. Jeong, A. Joung, H. J. Cho, S. H. Kim, and H. J. Kim, “Leptomeningeal metastasis: clinical experience of 519 cases,” European Journal of Cancer, vol. 56, pp. 107–114, 2016.

[10] C. Wang, X. Lu, Z. Lyu, N. Bi, and L. Wang, “Comparison of up-front radiotherapy and TKI with TKI alone for NSCLC with brain metastases and EGFR mutation: a meta-analysis,” Lung Cancer, vol. 122, pp. 94–99, 2018.

[11] Y. Wang, S. Liu, X. Wei et al., “Non-small cell lung cancer leptomeningeal metastases treated with intrathecal therapy plus osimertinib and temozolomide and whole-brain radiation therapy: a case report,” Oncotargets and Therapy, vol. 11, pp. 4733–4738, 2018.

[12] Y. Ju, S. Sun, J. Wang, and S. jiao, “Prolonged overall survival of patients with leptomeningeal carcinomatosis from nonsmall cell lung cancer,” Journal of Cancer Research and Therapeutics, vol. 12, no. 5, p. 126, 2016.

[13] N. Girard, “Optimizing outcomes in EGFR mutation-positive NSCLC: which tyrosine kinase inhibitor and when?” Future Oncology, vol. 14, no. 11, pp. 1117–1132, 2018.

[14] G. Goss, C. M. Tsai, F. A. Shepherd et al., “CNS response to osimertinib in patients with T790M-positive advanced NSCLC: pooled data from two phase II trials,” Annals of Oncology, vol. 29, no. 3, pp. 687–693, 2018.

[15] Y. L. Wu, M. J. Ahn, M. C. Garassino et al., “CNS efficacy of osimertinib in patients with T790M-positive advanced non-small-cell lung cancer: data from a randomized phase III trial (AURA3),” Journal of Clinical Oncology, vol. 36, no. 26, pp. 2702–2709, 2018.

[16] L. Xie, S. Nagral, H. A. Wakelee, G. Li, S. G. Soltys, and J. W. Neal, “Osimertinib for EGFR-mutant non-small cell lung cancer with brain metastases: results from a single-center retrospective study,” The Oncologist, vol. 24, no. 6, pp. 836–843, 2019.

[17] B. C. Cho, B. Chewaskulyong, K. H. Lee et al., “Osimertinib versus standard of care EGFR TKI as first-line treatment in patients with EGFRm advanced NSCLC: FLAURA Asian subset,” Journal of Thoracic Oncology, vol. 14, no. 1, pp. 99–106, 2019.

[18] J. C. Soria, Y. Ohe, J. Vansteenkiste et al., “Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer,” The New England Journal of Medicine, vol. 378, no. 2, pp. 113–125, 2018.

[19] J. Vansteenkiste, T. Reungwetwattana, K. Nakagawa et al., “CNS response to osimertinib vs standard of care (SoC) EGFR-TKI as first-line therapy in patients (pts) with EGFR-TKI sensitising mutation (EGFRm)-positive advanced non-small cell lung cancer (NSCLC): data from the FLAURA study,” Annals of Oncology, vol. 28, Supplement 10, 2017.

[20] P. N. Aguiar Jr., B. Haaland, W. Park, P. San Tan, A. Del Giglio, and G. de Lima Lopes Jr., “Cost-effectiveness of osimertinib in the first-line treatment of patients with EGFR-mutated advanced non-small cell lung cancer,” JAMA Oncology, vol. 4, no. 8, pp. 1080–1084, 2018.

[21] A. Tamiya, M. Tamiya, T. Nishihara et al., “Cerebrospinal fluid penetration rate and efficacy of afatinib in patients with EGFR mutation-positive non-small cell lung cancer with leptomeningeal carcinomatosis: a multicenter prospective study,” Anticancer Research, vol. 37, no. 8, pp. 4177–4182, 2017.

[22] L. Paz-Ares, E. H. Tan, K. O’Byrne et al., “Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial,” Annals of Oncology, vol. 28, no. 2, pp. 270–277, 2017.

[23] S. R. Zhang, L. C. Zhu, Y. P. Jiang et al., “Efficacy of afatinib, an irreversible ErbB family blocker, in the treatment of intracerebral metastases of non-small cell lung cancer in mice,” Acta Pharmacologica Sinica, vol. 38, no. 2, pp. 233–240, 2017.

[24] M. Schuler, Y. L. Wu, V. Hirsh et al., “First-line afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases,” Journal of Thoracic Oncology, vol. 11, no. 3, pp. 380–390, 2016.

[25] A. Diaz-Serrano, P. Gella, E. Jimenez, I. Zugazagoitia, and L. Paz-Ares Rodriguez, “Targeting EGFR in lung cancer: current standards and developments,” Drugs, vol. 78, no. 9, pp. 893–911, 2018.

[26] Z. Chen, X. Liu, J. Zhao, H. Yang, and X. Teng, “Correlation of EGFR mutation and histological subtype according to the IASLC/ATS/ERS classification of lung adenocarcinoma,” International Journal of Clinical and Experimental Pathology, vol. 7, no. 11, pp. 8039–8045, 2014.

[27] M. Hochmair, “Medical treatment options for patients with epidermal growth factor receptor mutation-positive non-small cell lung cancer suffering from brain metastases and/or leptomeningeal disease,” Targeted Oncology, vol. 13, no. 3, pp. 269–285, 2018.

[28] H. Niu, J. Zhou, H. Maan, M. Markman, and J. Niu, “Treatment of leptomeningeal metastases in a patient with non-small cell lung cancer harboring EGFR T790M mutation,” Case Reports in Oncology, vol. 10, no. 3, pp. 840–845, 2017.

[29] Y. S. Li, B. Y. Jiang, J. J. Yang et al., “Leptomeningeal metastases in patients with NSCLC with EGFR mutations,” Journal of Thoracic Oncology, vol. 11, no. 11, pp. 1962–1969, 2016.

[30] H. Cheng and R. Perez-Soler, “Leptomeningeal metastases in non-small-cell lung cancer,” The Lancet Oncology, vol. 19, no. 1, pp. e43–e55, 2018.

[31] D. S. Ettinger, D. L. Aisner, D. E. Wood et al., “NCCN Guidelines Insights: non-small cell lung cancer, version 5.2018,” Journal of the National Comprehensive Cancer Network, vol. 16, no. 7, pp. 807–821, 2018.

[32] M. Hochmair, S. Holzer, and O. C. Burghuber, “Complete remissions in afatinib-treated non-small-cell lung cancer patients with symptomatic brain metastases,” Anti-Cancer Drugs, vol. 27, no. 9, pp. 914–915, 2016.