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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

The importance of re-biopsy in the era of molecular therapy for lung cancer

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SUMMARY

Introduction Recent epidemiological data highlight that lung cancer incidence and mortality rates remain alarmingly high globally for both men and women. Over the last 10 years, the evolution in treatment corresponds to identifying specific driver mutations within lung tumors and developing inhibitors targeting these mutations.

Case outline A 73-year-old woman was diagnosed with lung adenocarcinoma staged as T4N2M1b at the Institute for Pulmonary Diseases of Vojvodina in February 2019. The Oncology Board recommended molecular analysis of the tumor and palliative radiation therapy for spinal metastases. Molecular testing identified an exon 19 deletion in the epidermal growth factor receptor (*EGFR*) gene. Following radiation treatment of the spine metastases, the patient began treatment with afatinib in May 2019. After 35 cycles of the aforementioned therapy, in April 2022, a computed tomography scan of the thorax and abdomen showed that the disease had progressed. Despite three liquid biopsies failing to detect the T790M mutation, a subsequent bronchoscopy and tissue re-biopsy confirmed its presence, prompting the initiation of osimertinib treatment. Twelve months into osimertinib therapy, the patient continues to be monitored.

Conclusion *EGFR* is a crucial predictive biomarker for non-small cell lung cancer. The introduction of specific tyrosine kinase inhibitors – first-generation agents like gefitinib and erlotinib, second-generation afatinib, and introduction of third-generation (osimertinib or lolatinib) when initial treatments are met with resistance, has led to significant therapeutic breakthroughs.

Keywords: lung adenocarcinoma; liquid biopsy; T790M; tissue biopsy

INTRODUCTION

Current international guidelines recommend conducting molecular testing at the initial diagnosis of advanced non-small cell lung cancer (NSCLC), and it is considered obligatory for cases of lung adenocarcinoma (ADC) [1]. Over recent decades, there has been a significant increase in the identification of oncogenic drivers, facilitating the prediction of clinical responses to targeted therapies in NSCLC. The molecular characterization of lung ADC, as opposed to mere histological classification, has paved the way for fully personalized treatment strategies [2]. In 2004, the epidermal growth factor receptor (EGFR) was recognized as a predictive biomarker for NSCLC [3]. EGFR, a 170-kDa tyrosine kinase receptor and member of the ERbB family, has been associated with mutation-driven oncogenesis in NSCLC. Approximately 10–15% of NSCLC patients with mutations predominantly in exons 19 and 21 exhibit profound responses to targeted inhibition by first-generation tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib, the second-generation drug afatinib, and third-generation drugs like osimertinib and lorlatinib [4]. However, prolonged treatment with these TKIs can lead to the development of resistant neoplastic cells due to mutations in the targeted *EGFR* gene, consequently diminishing the initial high expectations for targeted therapy. Specific mechanisms which lead to acquired resistance to TKIs were uncovered. A notable example is the T790M mutation within the *EGFR* gene in lung ADC, which is found in over 50% of patients after treatment with first- or second-generation EGFR TKIs [5]. Subsequent generations of drugs, like osimertinib, have been designed to precisely target this specific mutation [6]. Re-biopsy of the lung tumor tissue has proven to be useful in identifying particular genetic changes and targeted mutations. This process offers more detailed information compared to liquid biopsy and is essential for reassessing patients to ensure the continuation of effective treatment [7]. Illustrating the potential for long-term success with this approach, we report the case of a female patient with metastatic ADC. After developing resistance to the first line of molecular therapy, she was administered a new generation TKI in her second-line treatment regimen, highlighting the evolving landscape of personalized cancer treatment.

CASE REPORT

A 73-year-old non-smoking female with a history of hypertension, complete right bundle

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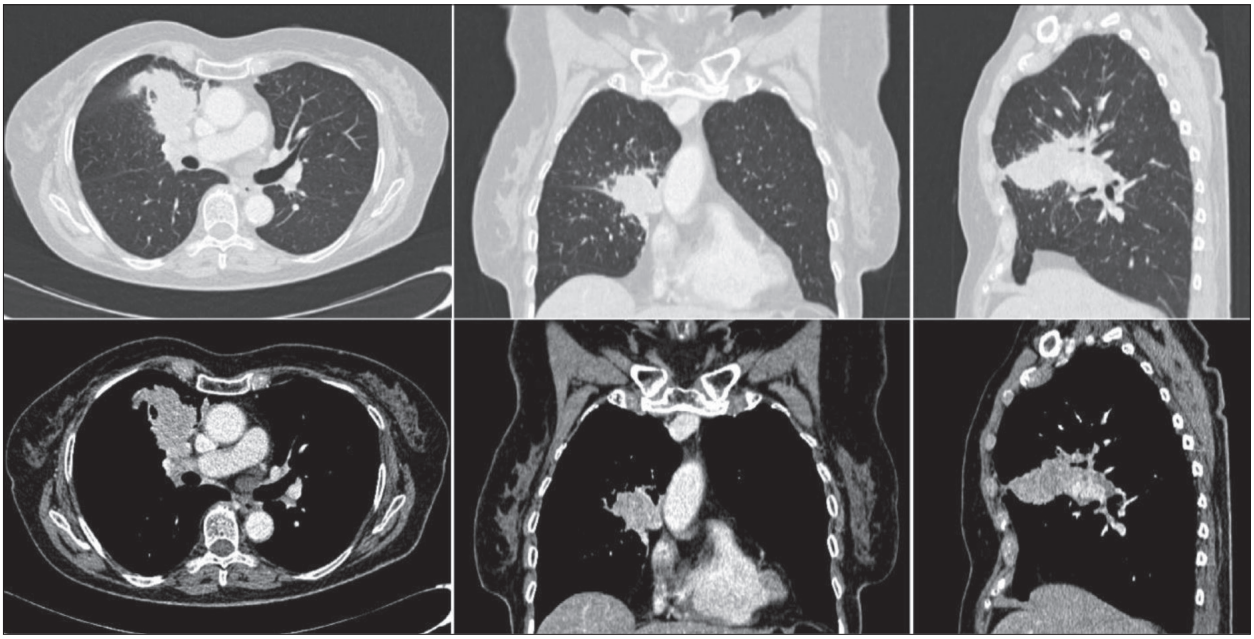

Figure 1. Initial chest CT at the time of diagnosis

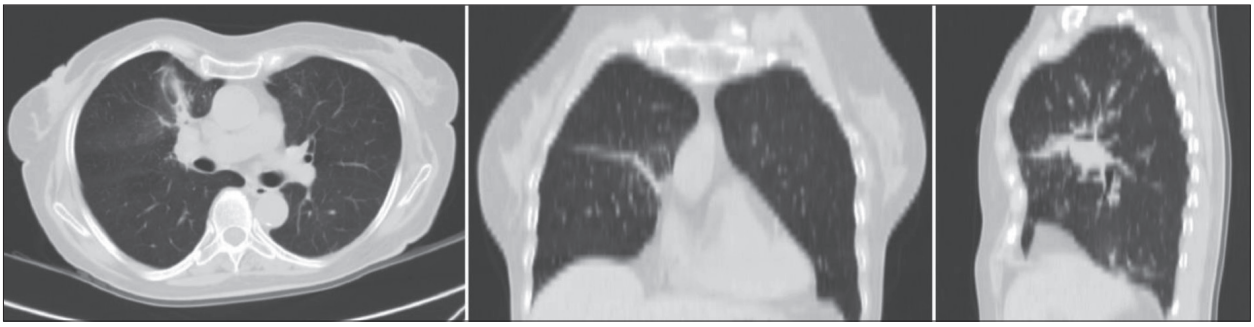

Figure 2. Chest CT after four months of treatment with afatinib

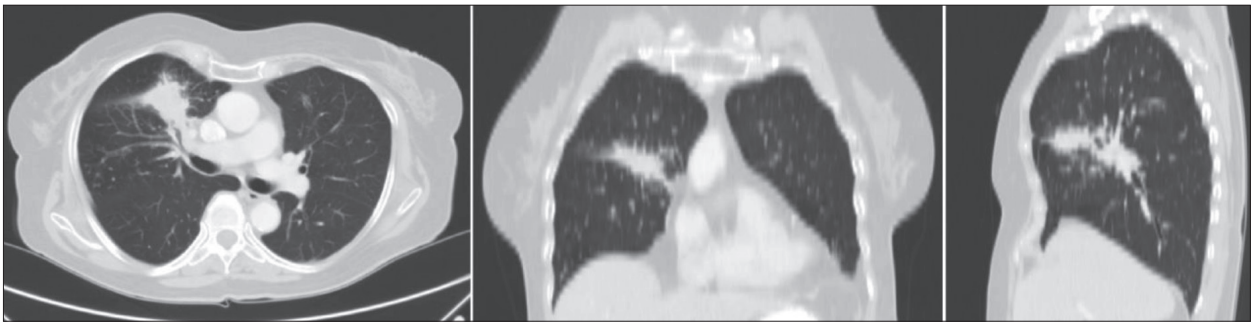

Figure 3. Chest CT at the time of disease progression to the drug afatinib

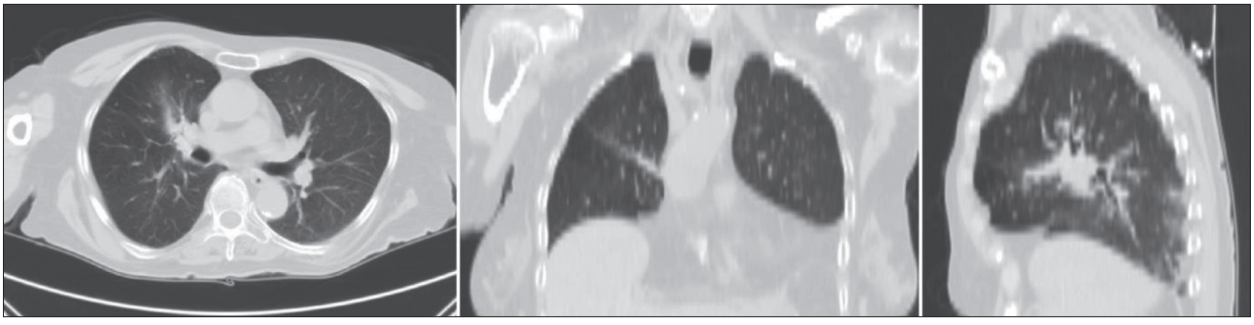

Figure 4. Chest CT after 12 months of treatment with osimertinib

branch block, and type 2 diabetes, developed symptoms in the form of difficulty breathing, and persistent dry cough in January 2019. An initial chest X-ray disclosed a sizable tumor, approximately 7 cm in diameter, located in the right parahilar region. Further investigation using a computed tomography (CT) scan of the chest and abdomen identified an infiltrative mass in the S3 segment of the right upper lung lobe, with dimensions of 78 × 53 mm. The lesion extended into the mediastinal pleura, mediastinal fatty tissue, and interlobar fissure, accompanied by pronounced pneumonitis and lymphangitis. Additionally, bilateral nodular alterations in the lung were evident (Figure 1). There was a suspicion of involvement with potential secondary deposits in the left iliac bone, as well as vertebral levels, VTh11 and VL3–5.

In February 2019, bronchoscopy was performed and the cytological analysis of samples obtained via transbronchial needle aspiration of tumor bronchial compression confirmed the presence of lung ADC. The disease was clinically and radiologically staged as T4N2M1b. In the following month, March 2019, the Oncology Board at the Institute for Pulmonary Diseases of Vojvodina (OB IPBV) recommended molecular testing of the tumor biopsy to identify potential targets for therapy. The patient's tumor sample was tested for *EGFR* mutations using the Cobas EGFR Mutation Test v2 (CE-IVD). This test confirmed a deletion in exon 19 of the *EGFR* gene. In April 2019, the patient underwent conformal radiation therapy, targeting the tumor metastases in the thoracic and lumbar vertebrae. Following radiotherapy, the patient began treatment with afatinib in May 2019. The first follow-up CT scan of the chest and abdomen in July 2019, assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, documented partial regression of both target and non-target lesions (Figure 2), indicating a positive response to the afatinib therapy.

For an extended period of 35 months from the beginning of afatinib therapy, according to RECIST criteria, stable disease was observed on all control findings of the CT of the chest and abdomen. In April 2022, however, a chest and abdomen CT scan showed a progression of the disease per RECIST criteria (Figure 3).

In May and June 2022, a liquid biopsy was carried out on the patient's blood plasma to check for *EGFR* mutation status. These tests reaffirmed the presence of a deletion in exon 19 of the *EGFR* gene, while at the same time, the circulating tumor DNA (ctDNA) plasma result was negative for the T790M mutation. The progression of the disease at this stage was classified as oligoprogression and the decision was made to continue with the afatinib treatment. However, a subsequent CT scan of the chest and abdomen in July 2022 verified further disease progression according to the RECIST criteria. The OB IPBV suspended the administration of the drug afatinib and made a decision for repeated bronchoscopy and re-biopsy.

The bronchoscopy performed in August 2022 confirmed endoscopic evidence of disease progression. Subsequent pathohistological analysis confirmed the diagnosis of lung ADC. Molecular testing identified the previously detected deletion in exon 19 and an additional T790M mutation in exon 20. With the emergence of the T790M mutation, the OB IPBV advised initiating treatment with osimertinib, a third-generation EGFR TKI, as a second-line therapy. The patient has been adhering to the prescribed osimertinib regimen in October 2022. The latest check-up control CT scan of the thorax and abdomen was performed in September 2023, showing partial regression according to RECIST (Figure 4).

Summarized, the beginning of the application of molecular therapy in our patient in whom metastatic disease existed since the date of established the diagnose was in May 2019 as the first-line therapy with the drug afatinib for 35 months, and the second line of therapy with the drug osimertinib for 12 months, up to the date of publication of the paper. She feels well, regularly performs all daily activities, and has no side effects from the currently applied therapy.

We confirm that we have read the journal's position on issues involving ethical publication and affirm that this work is consistent with those guidelines. Written consent to publish all shown material was obtained from the patient.

DISCUSSION

According to the most recent epidemiological data, the global incidence of lung cancer remains alarmingly high. It is the most common cancer among men and the second most common one among women. In 2020, there were approximately 2.2 million new cases of lung cancer diagnosed worldwide [8]. NSCLC is the predominant form, and the past decade has seen significant advances in the treatment of lung cancer type due to the identification of driver mutations, facilitating a personalized approach to therapy [9]. Tyrosine kinase inhibitors targeting the EGFR (EGFR TKIs) have been notably effective in patients with mutations in the EGFR gene. Among these "positive patients," especially those with lung ADC, response rates to EGFR TKIs can be as high as 80%, with progression-free survival (PFS) typically ranging 10–14 months [5]. The most prevalent activating mutations in the EGFR gene are deletions in exon 19 and the L858R point mutation in exon 21, which combined make up over 80% of all known activating *EGFR* mutations [10]. The presence of deletions in exon 19 or the L858R point mutation in exon 21 of the *EGFR* gene correlates with an enhanced response to targeted therapy using EGFR TKIs [11]. For our patient, who was diagnosed with metastatic ADC of the lung, the OB IPBV recommended molecular profiling using the real-time PCR Cobas EGFR Mutation Test v2 (CE-IVD). This test is capable of detecting 42 distinct mutations across exons 18–21 of the *EGFR* gene, including the T790M resistance mutation, but it has a reduced sensitivity for detecting 50% of *EGFR* exon 20 insertion mutations when compared to the more comprehensive next-generation sequencing method, which our Institution has not yet adopted [12]. Upon receiving the molecular test results indicating an *EGFR* exon 19 deletion, our patient

commenced targeted treatment with a second-generation TKI afatinib. Second-generation TKIs, including afatinib and dacomitinib, have been evaluated in phase III randomized trials. Results from Lux-Lung 3, Lux-Lung 6, and Lux-Lung 7 trials consistently demonstrated a significantly longer median PFS for patients treated with afatinib [13]. For the patient discussed, the PFS reached impressive 35 months. Throughout this period, based on the RECIST version 1.1, our patient's follow-up imaging consistently showed either partial regression or stable disease.

Acquired resistance to EGFR TKIs eventually develops in most patients undergoing this treatment modality. Typically, resistance that is EGFR-dependent arises in patients who have been treated with first or second-generation TKIs. In contrast, resistance associated with third-generation TKIs occurs less frequently [14]. The T790M mutation in exon 20 of the *EGFR* gene is particularly notable, emerging in about 50–60% of patients treated with first- or second-generation TKIs. Interestingly, this mutation appears more commonly in patients who initially present with a deletion in exon 19 of the *EGFR* gene as opposed to those with the L858R mutation [15]. The detection of the T790M mutation can be conducted through two principal methods: a liquid biopsy of the patient's blood plasma or a re-biopsy of the tumor tissue. By examining blood plasma or other bodily fluids such as pleural effusion, circulating tumor DNA (ctDNA) carrying the mutation can be identified. However, the sensitivity of liquid biopsies might be lower in some metastatic lung ADC since ctDNA might not be present in large quantities in peripheral blood, which can lead to false-negative results. For the patient in question, three liquid biopsies failed to detect the T790M mutation, yet a re-biopsy of the tumor obtained during a new bronchoscopic procedure did reveal the mutation in exon 20 and the T790M mutation. In the AURA2 study, the sensitivity and specificity of liquid biopsy for detecting the T790M mutation were 61% and 79%, respectively, compered to tissue biopsy, which boasts a higher sensitivity of 90% and a specificity of 91% [16]. The AURA2 study explored the efficacy and safety of osimertinib, a third-generation EGFR TKI, for patients who had developed resistance to first- and second-line EGFR TKI treatments and had the T790M mutation in exon 20 of the *EGFR* gene. AURA3 phase III clinical trial demonstrated that for patients harboring the T790M mutation and treated with osimertinib, the median PFS ranged 10.1–14.2 months [17]. The detection of T790M mutations varies based on the method employed: 30–40% are identified through pathological or cytological examination of tumor tissue, while plasma samples account for about 20% of detections [18]. This disparity highlights the ongoing need to re-biopsy using refined diagnostic tools to ensure accurate mutation status assessment and to guide therapeutic decision-making.

Conflict of interest: None declared.

REFERENCES

1. Kalemkerian GP, Narula N, Kennedy EB, Biermann WA, Donington J, Leighl NB, et al. Molecular testing guideline for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors: American society of clinical oncology endorsement of the college of American pathologists/ international association for the. J Clin Oncol. 2018;36(9):911–9. [DOI: 10.1200/JCO.2017.76.7293] [PMID: 29401004]
2. Passiglia F, Scagliotti GV. The evolving paradigm of precision medicine in lung cancer. Curr Opin Pulm Med. 2021;27(4):249–54. [DOI: 10.1097/MCP.0000000000000778] [PMID: 33927132]
3. Jurišić V, Obradovic J, Pavlović S, Djordjevic N. Epidermal Growth Factor Receptor Gene in Non-Small-Cell Lung Cancer: The Importance of Promoter Polymorphism Investigation. Anal Cell Pathol (Amst). 2018;2018:6192187. [DOI: 10.1155/2018/6192187] [PMID: 30406002]
4. Greenhalgh J, Dwan K, Boland A, Bates V, Vecchio F, Dundar Y, et al. First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer. Cochrane Database Syst Rev. 2016(5):CD010383. [DOI: 10.1002/14651858.CD010383.pub2] [PMID: 27223332]
5. Holleman MS, van Tinteren H, Groen HJM, Al MJ, Uyl-de Groot CA. First-line tyrosine kinase inhibitors in EGFR mutation-positive non-small-cell lung cancer: A network meta-analysis. Onco Targets Ther. 2019;12:1413–21. [DOI: 10.2147/OTT.S189438] [PMID: 30863108]
6. Wu SG, Shih JY. Management of acquired resistance to EGFR TKI-targeted therapy in advanced non-small cell lung cancer. Mol Cancer. 2018;17(1):38. [DOI: 10.1186/s12943-018-0777-1] [PMID: 29455650]
7. Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, et al; AURA3 Investigators. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med. 2017;376(7):629–40. [DOI: 10.1056/NEJMoa1612674] [PMID: 27959700]
8. Mondoni M, Rinaldo RF, Carlucci P, Terraneo S, Saderi L, Centanni S, et al. Bronchoscopic sampling techniques in the era of technological bronchoscopy. Pulmonology. 2022;28(6):461–71. [DOI: 10.1016/j.pulmoe.2020.06.007] [PMID: 32624385]
9. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73(1):17–48. [DOI: 10.3322/caac.21763] [PMID: 36633525]
10. Winfree KB, Molife C, Peterson PM, Chen Y, Visseren-Grul CM, Leusch MS, et al. Real-world characteristics and outcomes of advanced non-small-cell lung cancer patients with EGFR exon 19 deletions or exon 21 mutations. Future Oncol. 2021;17(22):2867–81. [DOI: 10.2217/fon-2021-0218] [PMID: 33866796]
11. Lindeman NI, Cagle PT, Aisner DL, Arcila ME, Beasley MB, Bernicker EH, et al. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. J Mol Diagn. 2018;20(2):129–59. [DOI: 10.1016/j.jmoldx.2017.11.004] [PMID: 29398453]
12. Bauml JM, Viteri S, Minchom A, Bazhenova L, Ou S, Schaffer M, et al. FP07.12 Underdiagnosis of EGFR Exon 20 Insertion Mutation Variants: Estimates from NGS-based Real-World Datasets. J Thorac Oncol. 2021;16(3):S208–9. [DOI: 10.1016/j.jtho.2021.01.112]
13. Paz-Ares L, Tan EH, O'Byrne K, Zhang L, Hirsh V, Boyer M, 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. Ann Oncol. 2017;28(2):270–7. [DOI: 10.1093/annonc/mdw611] [PMID: 28426106]
14. Westover D, Zugazagoitia J, Cho BC, Lovly CM, Paz-Ares L. Mechanisms of acquired resistance to first- and second-generation EGFR tyrosine kinase inhibitors. Ann Oncol. 2018;29(suppl_1):i10–i19. [DOI: 10.1093/annonc/mdx703] [PMID: 29462254]
15. Passaro A, Jänne PA, Mok T, Peters S. Overcoming therapy resistance in EGFR-mutant lung cancer. Nat Cancer. 2021;2(4):377–91. [DOI: 10.1038/s43018-021-00195-8] [PMID: 35122001]

16. Goss G, Tsai CM, Shepherd FA, Bazhenova L, Lee JS, Chang GC, et al. Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol. 2016;17(12):1643–52. [DOI: 10.1016/S1470-2045(16)30508-3] [PMID: 27751847]
17. Lee JH, Kim EY, Park CK, Lee SY, Lee MK, Yoon SH, et al. Real-World Study of Osimertinib in Korean Patients with Epidermal Growth Factor Receptor T790M Mutation-Positive Non-Small Cell Lung Cancer. Cancer Res Treat. 2023;55(1):112–22. [DOI: 10.4143/crt.2022.381] [PMID: 36049499]
18. Hong MH, Kim HR, Ahn BC, Heo SJ, Kim JH, Cho BC. Real-World Analysis of the Efficacy of Rebiopsy and EGFR Mutation Test of Tissue and Plasma Samples in Drug-Resistant Non-Small Cell Lung Cancer. Yonsei Med J. 2019;60(6):525–34. [DOI: 10.3349/ymj.2019.60.6.525] [PMID: 31124335]

Значај ребиопсије у ери молекуларне терапије карцинома плућа

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САЖЕТАК

Увод Према последњим епидемиолошким подацима, инциденца карцинома плућа у свету је и даље висока, као и стопе морталитета за оба пола. Пре више од деценије, открићем такозваних покретачких мутација у ткиву тумора омогућено је терапијско деловање њиховим инхибиторима.

Приказ болесника Код болеснице старости 73 године је у фебруару 2019. године бронхоскопијом у Институту за плућне болести Војводине дијагностикован аденокарцином плућа, клиничко-радиолошког стадијума болести *cT4N2M1b*. Онколошки конзилијум Института за плућне болести Војводине донео је одлуку за молекуларно тестирање ткива тумора и примену палијативног зрачења метастаза у кичми. Тестирањем рецептора епидермалног фактора раста добијен је резултат делеције у егзону 19. После примењене зрачне терапије на метастазе у кичменим пршљеновима, у мају 2019. године започета је терапија применом лека афатиниб. На компјутеризованој томографији торакса и абдомена у априлу 2022. описана је прогресија болести. Упркос томе што три течне биопсије нису успеле да открију мутацију тумора T790M, накнадна бронхоскопија и ребиопсија потврдиле су њено присуство у ткиву тумора и отпочела је терапија леком осимертинибом. До објављивања рада болесница је била 12 месеци на терапији леком осимертинибом.

Закључак Рецептор епидермалног фактора раста је предиктивни биомаркер за немикроцелуларни карцином плућа. Примењени специфични инхибитори тирозинске киназе прве генерације као што су лекови гефитиниб, ерлотиниб, друге генерације – лек афатиниб појавом резистенције тумора на инхибиторе тирозинске киназе, треће генерације – лекови осимертиниб и лорлатиниб, дају одличне терапијске одговоре.

Кључне речи: аденокарцином плућа; течна биопсија; T790M; ткивна биопсија