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The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

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EDITORIAL

Advanced lung adenocarcinoma with *EGFR* 19-del mutation transforms into squamous cell carcinoma after *EGFR* tyrosine kinase inhibitor treatment

Ruo-Bing Qi, Zheng-Hao Wu

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Abstract

In this editorial we comment on the article by Ji *et al*. We focus specifically on the EGFR tyrosine kinase inhibitor (EGFR-TKI) treatment and the development of drug resistance to EGFR-TKIs.

Key Words: Lung adenocarcinoma; Squamous cell carcinoma; Histological transformation; Epidermal growth factor receptor tyrosine kinase inhibitor; Drug resistance

Core Tip: Patients treated with EGFR tyrosine kinase inhibitors (EGFR-TKIs) will inevitably face resistance issues, and resistance to EGFR-TKIs can be divided into two categories: Primary and acquired. Pathological transformation is one of the mechanisms for acquired resistance to EGFR-TKIs, with the transformation to squamous cell carcinoma being relatively rare. This case report provides detailed information on a 67-year-old female patient with advanced lung adenocarcinoma and an *EGFR* 19del mutation who developed resistance after treatment with EGFR-TKIs.

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INTRODUCTION

Lung cancer is a major cause of cancer-related deaths, ranking[1]. Non-small cell lung cancer (NSCLC), as the most prevalent histological subtype of lung cancer, includes squamous cell carcinoma (LUSC) and adenocarcinoma (LUAD) [2]. For the treatment of early-stage NSCLC patients, surgical resection is often prioritized. In contrast, chemotherapy is more commonly used for advanced NSCLC patients. For NSCLC patients with specific gene mutations (such as epidermal growth factor receptor [EGFR] L858R mutation and *EGFR* exon 19 deletion), molecular targeted therapy is commonly employed. Particularly, for patients with EGFR-sensitizing mutations, EGFR tyrosine kinase inhibitors (EGFR-TKIs) are often prioritized[3-6]. Due to the development and clinical application of EGFR-TKIs, the survival and clinical outcomes of NSCLC patients with EGFR mutations have significantly improved. Therefore, although there are many treatment options available for NSCLC patients with EGFR mutations, EGFR-TKIs remain the standard and most commonly used first-line treatment[7,8].

Although EGFR-TKIs can significantly improve the survival rate of NSCLC patients with EGFR-sensitizing mutations, it is inevitable that patients will encounter resistance issues after receiving EGFR-TKI treatment for a period of time, thus limiting its treatment efficacy and leading to disease progression. Previous research by our study group and other researchers has indicated that pathological transformation is one of the mechanisms underlying acquired resistance to EGFR-TKIs, particularly in cases where advanced lung adenocarcinoma transforms into squamous cell carcinoma following treatment with EGFR-TKIs for the former.

Resistance to therapy is challenging for the effective treatment of most tumors. Clinically, first- and second-generation EGFR-TKIs (gefitinib, dacomitinib, and afatinib) are often used for tumor treatment. Specifically, for NSCLC patients with *EGFR* gene mutations, the third-generation EGFR-TKI osimertinib is usually the preferred treatment. However, many patients still experience disease progression due to the development of acquired resistance to TKIs[9-12].

The purpose of this editorial is to discuss the mechanisms underlying resistance of EGFR-mutant NSCLC to TKIs and to review the literature on the transformation to squamous cell carcinoma following EGFR-TKI treatment for lung adenocarcinoma.

EGFR signaling is a driver of tumor growth because multiple proteins of this pathway are involved in multiple pathways, causing mutual interference of different pathways and thereby affecting pathway selection. This ultimately leads to amplification and mutations, allowing tumors to escape the inhibition by TKI monotherapy and resulting in the limitations of this treatment method[13].

In a previous study[14], pathological tissue biopsy confirmed squamous cell carcinoma transformation. This finding may also explain why the patient developed drug resistance[14]. In the paper by Ji *et al*[15], it was speculated that after EGFR-TKI treatment, adenocarcinoma component was inhibited and gradually underwent apoptosis, while squamous cell carcinoma component continued to proliferate and gradually became the dominant component, thus resulting in the transformation from adenocarcinoma to squamous cell carcinoma in the process of treatment.

DISCUSSION

There is a significant and close correlation between specific subtypes of lung cancer (such as LUAD and LUSC) and the abnormal increase of serum tumor markers. Therefore, detection of serum tumor markers can be used to assist in the diagnosis of lung cancer types. Regarding the lack of a significant correlation between the transformation of squamous cell carcinoma and changes in serum levels of squamous cell carcinoma associated antigens mentioned in the paper by Ji *et al*[15], more substantial evidence is still needed to confirm this.

CONCLUSION

The use of EGFR-TKIs has greatly improved EGFR-mutated NSCLC. However, the majority of these patients develop acquired resistance *via* a variety of mechanisms, including secondary mutations in EGFR, phenotypic shifts, and activation of bypass signaling pathways[16,17]. For EGFR-mutated NSCLC patients who have failed EGFR-TKI treatment, there is still an unmet need for new treatment options. For these patients, it is necessary to confirm whether acquired resistance has occurred. If acquired resistance is present, molecular analysis should be conducted to determine the specific causes of resistance. Based on these findings, patients can then participate in clinical trials for relevant treatments[18].

FOOTNOTES

Author contributions: Qi RB designed the research study, analyzed the data, and wrote the manuscript; Wu ZH performed the research; Qi RB and Wu ZH contributed new reagents and analytic tools; all authors have read and approved the final manuscript.

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