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CASE REPORT

Neoadjuvant Targeted Therapy with Dacomitinib in a Stage IIIA Non-Small-Cell Lung Cancer Patient Harboring *EGFR* G719X: A Case Report

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Abstract: The effectiveness of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) has been established, leading the NCCN Guidelines to recommend it as a first-line treatment for patients with advanced *EGFR* mutation-positive non-small cell lung cancer (NSCLC). However, there is still controversy about the use of neoadjuvant TKI treatment for patients with stage III EGFR mutation-positive NSCLC. Here, we firstly report that a stage IIIA lung adenocarcinoma patient benefited from chemotherapy and dacomitinib as neoadjuvant targeted therapy based on *EGFR* G719X mutation, achieving a pathological downstaging and the chance of radical surgical resection. Our case describes dacomitinib use as neoadjuvant targeted therapy for EGFR positive advanced NSCLC and highlights the application of molecular testing for the better treatment decision making.

Keywords: uncommon EGFR mutations, *EGFR* G719X, neoadjuvant targeted therapy, dacomitinib, NSCLC

Introduction

For advanced non-small cell lung cancer (NSCLC) patients with common epidermal growth factor receptor (*EGFR*) mutations (exon 19 deletions or the exon 21 L858R mutation), EGFR tyrosine kinase inhibitors (TKIs) are the standard therapies.[1] In addition, major uncommon *EGFR* mutations, such as G719X, S768I, and L861Q, have shown sensitivity to *EGFR*-TKIs, especially the second-generation TKI.[2] Dacomitinib is a highly selective second-generation EGFR-TKI that irreversibly blocks signaling from both heterodimers and homodimers of all members of the human EGFR family.[3] Dacomitinib has potential applications for patients with rare mutations.[4,5] In addition, dacomitinib demonstrated strong effectiveness in patients with brain metastases, while also posing a relatively low risk of side effects.[5] In a Chinese cohort study, dacomitinib demonstrated potential efficacy with manageable toxicity in advanced NSCLC patients harboring major uncommon *EGFR* mutations (G719X/S768I/L861Q).[6]

Most patients with stage III NSCLC have missed the opportunity for radical surgery at the time of initial diagnosis. In recent years, neoadjuvant and adjuvant targeted therapy has offered a convenient treatment option for NSCLC patients with *EGFR* mutations.[7] In these patients, neoadjuvant targeted therapy is significantly more effective than chemotherapy, leading to a more noticeable reduction in the size of the primary tumor. This makes patients more likely to be eligible for radical surgery.[8] Additionally, adjuvant targeted therapy provides a convenient treatment option, allowing patients to benefit from improved survival outcomes.[8] Here, we firstly reported a patient with stage III NSCLC carried *EGFR* G719X, who was successfully treated with surgical resection following dacomitinib as neoadjuvant targeted therapy.

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Case Presentation

A 54-year-old Chinese male with 30 years of smoking history presented with a worsening cough for 3 months, with a performance status score of 1. In April 2023, an enhanced computed tomography (CT) revealed a 22 mm × 12 mm × 16 mm mass in the right upper lobe with invasion in the right hilum and mediastinal (Figure 1A and B), which were confirmed by positron emission tomography-CT (PET-CT) scan. Immunohistochemistry (IHC) analysis of the biopsy from the lesion in the upper right lobe of the lung was positive for TTF-1, NpA, CK7, CD5/6 and Ki67 (60%); and negative for p40, p63 and CD56. The patient was diagnosed with stage IIIA lung adenocarcinoma (cT1cN2M0). The follow-up targeted NGS analysis of his lung lesion biopsy identified an *EGFR* G719X with a mutant allele frequency (MAF) of 3.8%. After a multiple disciplinary team (MDT) discussion, the initial tumor was considered unresectable due to metastasis in the right hilum and mediastinum. In May 2023, two cycles of PC chemotherapy (pemetrexed with 0.9g d1 and carboplatin with 600mg d1) and dacomitinib (30mg) were given. The chest CT showed obvious shrinkage in the lesions in the right upper lung lobe and the lymph nodes of the mediastinum, contributing to partial response (PR) (Figure 1B). In July 2023, video-assisted thoracic surgery (VATS) with right upper lobectomy was performed. Intraoperative exploration revealed that the tumor was located in the right upper lobe, measuring approximately 1.5*1.5 cm with unclear boundaries. The postoperative pathology results indicated that 10% of the tumor cells remained alive, surrounded by significant fibrosis, necrosis, as well as inflammatory and immune cells (Figure 2A and B). After chemotherapy and dacomitinib induction, there were no lymph node metastases, and the pathological stage was ypT1bN0M0. After the surgery, two cycles of PC chemotherapy were administered, followed by targeted therapy with dacomitinib as adjuvant treatment for 2 more years in accordance with the diagnosis and treatment guidelines. At the final follow-up in September 2024, no adverse events or disease progression had occurred. A progression-free survival (PFS) of more than 14 months was achieved.

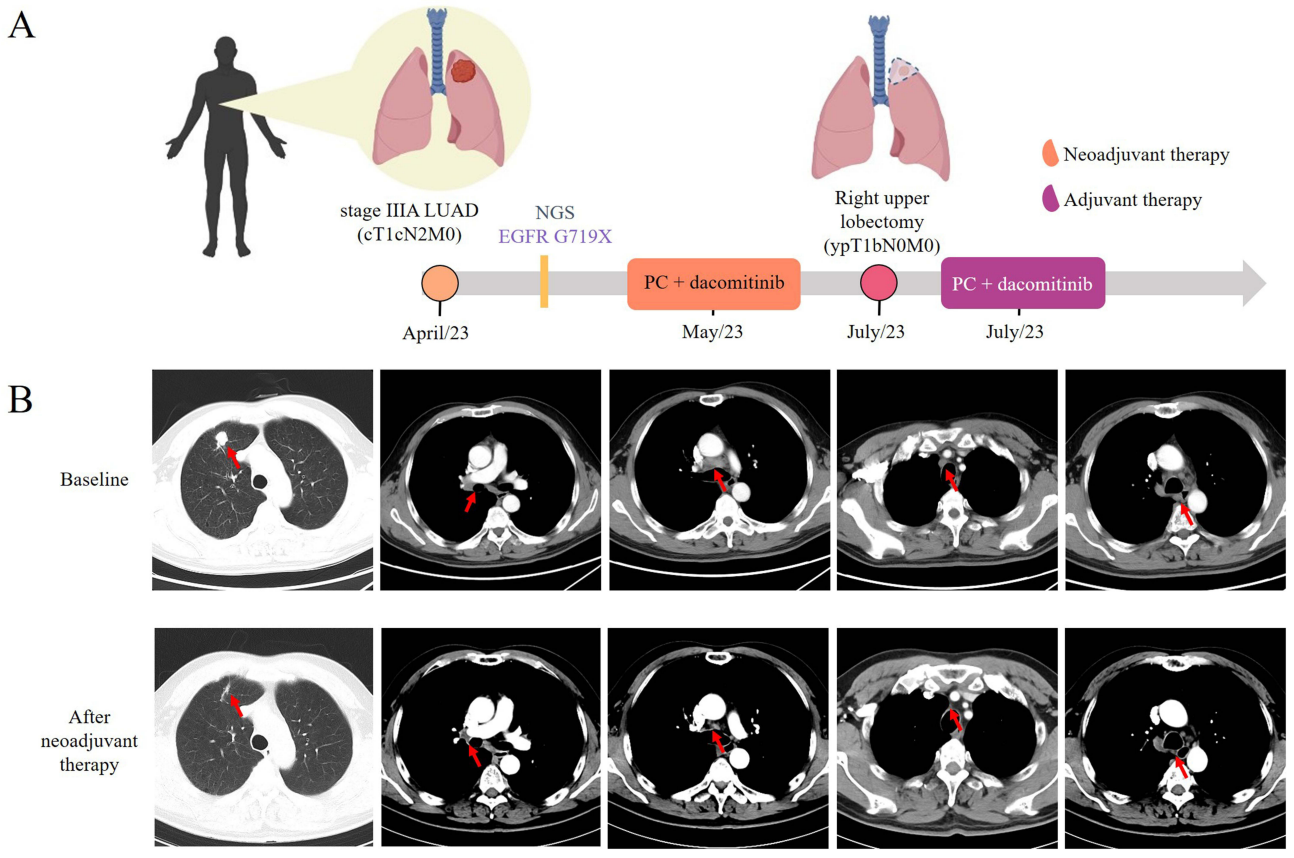

Figure 1 Representative clinical images during the treatment course. (**A**) Disease time line illustrated the different treatment received by the patient. (**B**) Radiological evaluation of the primary tumor and lymph nodes both at the baseline and after neoadjuvant therapy.
Abbreviations: LUAD, lung adenocarcinoma; NGC, next-generation sequencing; PC, pemetrexed and carboplatin.

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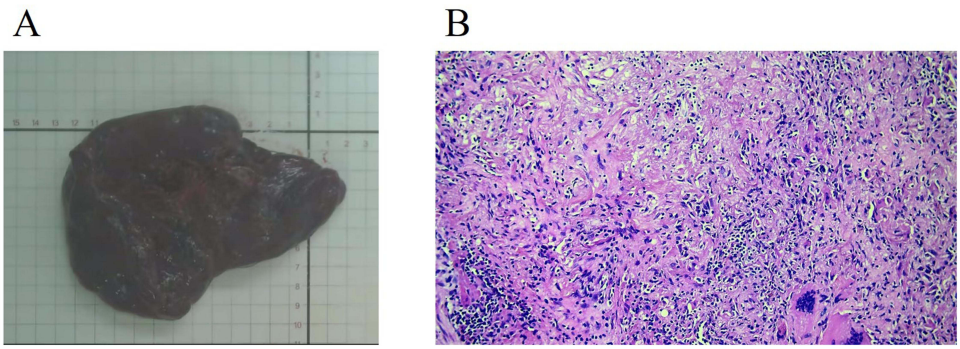

Figure 2 The photograph and hematoxylin and eosin (HE) staining for the lesions. (**A**) The photograph shows the lesion in the upper right lobe of the lung that was removed during surgery. (**B**) HE staining (200×) of the lesion in the upper right lobe of the lung following neoadjuvant therapy.

Discussion

Because stage III NSCLC is highly heterogeneous, a single treatment strategy may not sufficiently meet the clinical needs of all patients with this condition. Patients who are potentially operable may have the opportunity for radical resection through neoadjuvant therapies. Previous case reports have demonstrated the effectiveness of neoadjuvant targeted therapy in controlling the disease and achieving pathological downstaging in NSCLC.[8,9] To our knowledge, this is the first case of neoadjuvant chemotherapy and dacomitinib for NSCLC patients with *EGFR* G719X.

Approximately 50% of NSCLCs in Asians have the *EGFR* mutation. The G719X mutation occurs at exon 18 of the *EGFR* gene, including G719S, G719A, G719C and G719D.[10] The G719X mutation accounts for about 3% among all *EGFR* mutations and is considered an uncommon type of *EGFR* mutation.[11] G719X is considered moderately sensitive to first-generation EGFR-TKI.[10] However, it is more sensitive to the second-generation EGFR-TKI.[12,13] This sensitivity is due to the mutation increasing the distance between L718 and G796, which in turn makes the binding pocket for adenosine triphosphate more open and better able to interact with EGFR-TKIs.[14]

Dacomitinib is a highly selective and irreversible second-generation EGFR-TKI that inhibits all human EGFR signaling pathways. Some clinical trials have investigated its use in patients with advanced NSCLC with uncommon *EGFR* mutations, including G719X, L861X and S768I. Moreover, the adverse effects were found to be within acceptable and tolerable limits.[5] Dacomitinib could be a treatment option for patients with uncommon *EGFR* mutations in first-line therapy.

Previous studies demonstrated that neoadjuvant targeted therapy significantly benefits patients with *EGFR* mutation-positive stage IIIA NSCLC, offering advantages over neoadjuvant chemotherapy in terms of toxicity and tumor response rates.[15–17] Zhang et al reported on a patient diagnosed with right upper lung adenosquamous carcinoma (c-T3N2M0) who had an *EGFR* L858R mutation. The patient was treated with dacomitinib as neoadjuvant therapy and achieved a PR and a successful R0 resection.[18] The current literatures suggest that neoadjuvant therapy with EGFR-TKI increase the rate of radical surgical resection, reduce tumor volume and improve imaging response, but does not translate into disease downstaging or pathological remission.[19] However, in our case following chemotherapy and dacomitinib induction, pathological downstaging was observed. This might be due to the positive response of *EGFR* G719X to dacomitinib, so molecular testing and biomarker screening are necessary to optimize the clinical outcomes of targeted neoadjuvant therapy. The limitation of presenting a single case in this study should be noted. Thus, the efficacy and adverse events of the neoadjuvant chemotherapy and targeted therapy must be further evaluated in larger cohorts.

Conclusion

In summary, we reported the first case of a stage IIIA lung adenocarcinoma with an *EGFR* G719X mutation, who received the neoadjuvant chemotherapy and dacomitinib targeted therapy and achieved the pathological downstaging and the chance of radical surgical resection. This report provides a promising option for stage III *EGFR*-positive NSCLC. Moreover, we also highlighted the importance of molecular testing for the use of neoadjuvant targeted therapy. Because this study is based on a single case, additional clinical evidence is required for further investigation.

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Ethics Approval

Institutional approval was not required to publish the case details.

Consent for Publication

Written informed consent was obtained from the patient for publication of this paper and any accompanying images.

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Disclosure

The authors have no competing interests to declare.

References

1. Xue J, Li B, Wang Y, et al. Efficacy and safety of Epidermal Growth Factor Receptor (EGFR)-tyrosine kinase inhibitor combination therapy as first-line treatment for patients with advanced EGFR-mutated, non-small cell lung cancer: a systematic review and bayesian network meta-analysis. *Cancers*. 2022;14(19):4894. doi:10.3390/cancers14194894
2. Yang JC, Sequist LV, Geater SL, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-lung 2, LUX-lung 3, and lux-lung 6. *Lancet Oncol*. 2015;16:830–838. doi:10.1016/S1470-2045(15)00026-1
3. Lavacchi D, Mazzoni F, Giaccone G. Clinical evaluation of dacomitinib for the treatment of metastatic non-small cell lung cancer (NSCLC): current perspectives. *Drug Design, Develop Ther*. 2019;13:3187–3198. doi:10.2147/DDDT.S194231
4. Nishino M, Suda K, Kobayashi Y, et al. Effects of secondary EGFR mutations on resistance against upfront osimertinib in cells with EGFR-activating mutations in vitro. *Lung Cancer*. 2018;126:149–155. doi:10.1016/j.lungcan.2018.10.026
5. Pu X, Zhou Y, Kong Y. Efficacy and safety of dacomitinib in treatment-naïve patients with advanced NSCLC harboring uncommon EGFR mutation: an ambispective cohort study. *BMC Cancer*. 2023;23:982. doi:10.1186/s12885-023-11465-2
6. Li HS, Yang GJ, Cai Y, et al. Dacomitinib for advanced non-small cell lung cancer patients harboring major uncommon EGFR alterations: a dual-center, single-arm, ambispective cohort study in China. *Front Pharmacol*. 2022;13:919652.
7. Sequist LV, Willers H, Lanuti M, et al. The ASCENT trial: a Phase II study of neoadjuvant afatinib, chemoradiation and surgery for stage III EGFR mutation-positive NSCLC, American society of clinical oncology. *J Clin Oncol*. 2018;36
8. Xie X-H, Zhan Z-J, Qin -Y-Y, et al. Case report: neoadjuvant and adjuvant crizotinib targeted therapy in stage IIIA-N2 ALK-positive non-small-cell lung cancer. *Front Oncol*. 2021;11:655856.
9. Zhao S, Zhu S, Lei X, et al. Use of crizotinib as neoadjuvant therapy for non-small cell lung cancers patient with ROS1 rearrangement: a case report. *Thorac Cancer*. 2021;12:2815–2818
10. Li K, Yang M, Liang N, Li S. Determining EGFR-TKI sensitivity of G719X and other uncommon EGFR mutations in non-small cell lung cancer: perplexity and solution (Review). *Oncol Rep*. 2017;37:1347–1358. doi:10.3892/or.2017.5409
11. Cai Y, Wang Y, Sun J. Successful treatment of a patient with NSCLC carrying uncommon compound EGFR G719X and S768I mutations using osimertinib: a case report. *J Int Med Res*. 2020;48:300060520928793. doi:10.1177/0300060520928793
12. Kobayashi Y, Mitsudomi T. Not all epidermal growth factor receptor mutations in lung cancer are created equal: perspectives for individualized treatment strategy. *Cancer Sci*. 2016;107:1179–1186. doi:10.1111/cas.12996
13. Morita A, Hosokawa S, Yamada K, et al. Dacomitinib as a retreatment for advanced non-small cell lung cancer patient with an uncommon mutation. *Thorac Cancer* 2021;12:1248–1251
14. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *New Eng J Med*. 2004;350:2129–2139. doi:10.1056/NEJMoa040938
15. Chen D, Jin Z, Zhang J, et al. Efficacy and safety of neoadjuvant targeted therapy vs. neoadjuvant chemotherapy for stage IIIA EGFR-mutant non-small cell lung cancer: a systematic review and meta-analysis. *Front Surg*. 2021;8.
16. Sun L, Guo Y-J, Song J, et al. Neoadjuvant EGFR-TKI therapy for EGFR-mutant NSCLC: a systematic review and pooled analysis of five prospective clinical trials. *Front Oncol* 2021;10.
17. Lv C, Ma Y, Feng Q, et al. Does neoadjuvant targeted therapy provide an opportunity for resectable EGFR-mutant lung cancer: a real-world retrospective study. *J Thorac Dis*. 2020;12:5324–5335. doi:10.21037/jtd-20-1265
18. Zhang N, Chen S, Guo L, Chen XJAOPM. A case report of right upper lung adenosquamous carcinoma resection following neoadjuvant targeted therapy. *Ann Palliat Med* 2021;10(2021):4987–4993.
19. Liu W, Ren S, Xiao Y, Yang L, Zeng C, Hu Y. Neoadjuvant targeted therapy for resectable EGFR-mutant non-small cell lung cancer: current status and future considerations. *Front Pharmacol* 2022;13:1036334.