Clinical Oncology: Case Reports

Case Report A SCITECHNOL JOURNAL

Neoadjuvant and Adjuvant Crizotinib Targeted Therapy in Stage Iiia-N2 Alk-Positive Non-Small-Cell Lung Cancer

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Received date: 07 July, 2022, Manuscript No. COCR-22-69016;

Editor assigned date: 11 July, 2022, PreQC No. COCR-22-69016 (PQ);

Reviewed date: 18 July, 2022, QC No. COCR-22-69016;

Revised date: 26 July, 2022, Manuscript No. COCR-22-69016 (R);

Published date: 04 August, 2022, DOI: 10.4172/COCR.1000250

Abstract

Background: Patients with stage III non-small-cell lung cancer (NSCLC) should receive multimodality therapies. Radical surgical is recommended for resectable patients. Potentially resectable patients can gain opportunities for radical surgery through neoadjuvant treatments including chemotherapy, radiotherapy, or a combination of the two. Additionally, concurrent radical chemoradiotherapy followed by immunotherapy maintenance is preferred for unresectable patients. However, whether targeted therapy is superior to traditional chemotherapy for neoadjuvant or adjuvant treatments in patients with gene mutations remains unclear.

Keywords: Clinical oncology, Non-small-cell lung cancer

Introduction

According to the report of the international agency for research on cancer, 2,093,876 cases of lung cancer were newly diagnosed worldwide in 2018, accounting for 11.6% of newly diagnosed cancers in the same year [1]. Approximately 85% of lung cancers are classified as Non-Small-Cell Lung Cancer (NSCLC), and 30% of which are defined as stage III at diagnosis [2,3].

Stage III NSCLC is considered highly heterogeneous. Most patients have lost the opportunity for radical surgery at the time of initial diagnosis. The overall clinical efficacy of treatment for stage III NSCLC is not satisfactory, with 5-year survival rates of only 13 ~ 36% despite multimodality treatments [4,5]. In recent years, as small-molecule Tyrosine Kinase Inhibitors (TKIs) have been widely used in patients with advanced NSCLC with genetic mutations, the survival outcomes of patients have become highly promising, and the benefits are obvious [6-9], reflecting the need to explore the application of small-molecule TKIs in locally advanced NSCLC with genetic mutations.

For locally advanced NSCLC with Epidermal Growth Factor Receptor (EGFR) mutation, previous studies have focused on the application of neoadjuvant and adjuvant targeted therapy, and the results are promising. Among these patients, neoadjuvant targeted therapy is significantly superior to chemotherapy, and the regression of the primary tumor is more pronounced, rendering patients more likely to be eligible for radical surgery. Adjuvant targeted therapy offers a convenient treatment option, and patients can also benefit from survival outcomes [10]. However, no randomized controlled trial for patients with Anaplastic Lymphoma Kinase (ALK)-positive locally advanced NSCLC has been reported. The value of neoadjuvant and adjuvant targeted therapy remains unclear and requires further exploration. This case report describes initial crizotinib use as neoadjuvant and adjuvant targeted therapy for an ALK-positive locally advanced NSCLC patient [10].

Case Presentation

In April 2015, a 27-year-old male who presented with cough and phlegm was diagnosed with left upper lung adeno carcinoma by biopsy with a performance status score of 1. The patient's clinical stage was cT3N2M0 (stage IIIA, 7thUICC/AJCC). After preoperative evaluation, the initial tumor was considered unresectable since it was adjacent to the pericardium, and regional lymph node metastasis at the ipsilateral mediastinum was observed. Three cycles of gemcitabine (1250 mg/m2, day 1 and day 8) plus cisplatin (75 mg/m2, day 1) were given after diagnosis. Simultaneously, the tumor specimen was genetically tested and considered ALK-positive (Figure 1).

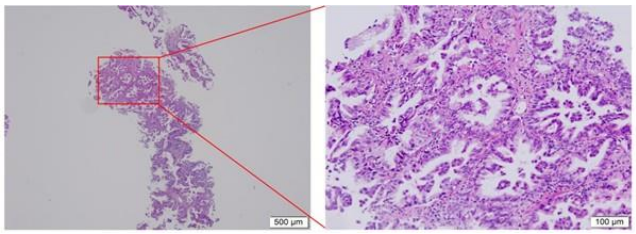

Figure A: Pretreatment biopsy the histological aspect of lung adenocarcinoma (HE staining).

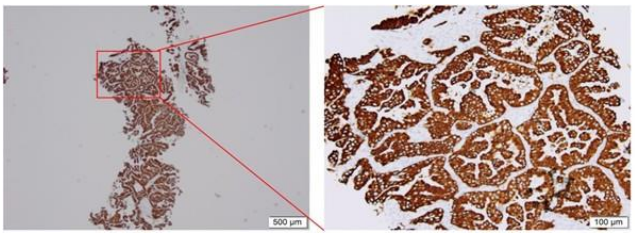

Figure B: Pretreatment biopsy the intense cytoplasmic ALK protein expression on immunohistochemistry.HE: Hematoxylin-Eosin; ALK: Anaplastic Lymphoma Kinase.

In Figure 2 the Contrast chest Computed Tomography (CT) after 3 cycles of gemcitabine plus cisplatin showed that the primary tumor remained stable according to the RECIST criteria compared with the initial CT scan (Figure A, B). Thereafter, crizotinib (250 mg, bid) was adopted, replacing the initial treatment. Encouragingly, the tumor was down staged to cT2aN2M0 within 2 months (Figure C).

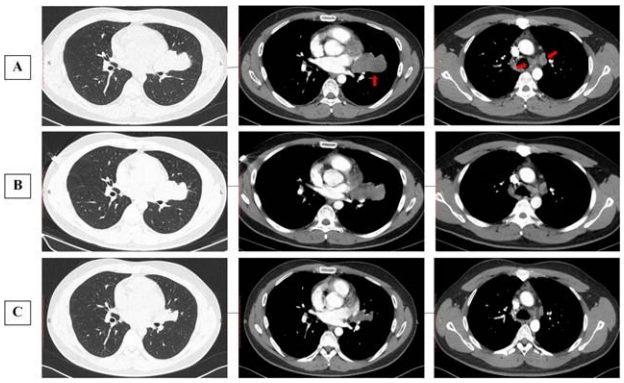

Figure 2: Radiological evaluation of the primary tumor and lymph nodes. (A) Baseline, (B) After 3 chemotherapy cycles, (C) After 2 months of crizotinib treatment.

In September 2015, Video-Assisted Thoracic Surgery (VATS) with left upper lobectomy plus lymph node dissection and partial pericardial resection was performed. The pathological stage was ypT2aN2M0. Then, Postoperative Radiotherapy (PORT) was performed with a total dose of 50 Gy in 25 fractions.

Crizotinib (250 mg, qd) was administered as adjuvant targeted therapy until an intracranial oligometastasis was first detected in July 2018, with a first Progression-Free Survival (PFS 1) time of 39 months. Subsequently, Stereotactic Radio Surgery (SRS) of the intracranial oligometastasis followed by crizotinib treatment (250 mg, bid) was performed. Five months after SRS, the intracranial oligometastasis showed a complete response based on the RECIST 1.1 criteria. At the final follow-up in May 2020, no grade 3/4 adverse events or disease progression had occurred. Remarkably, a second PFS time has not been reached. The patient's Overall Survival (OS) time is currently 61 months (Figure 3).

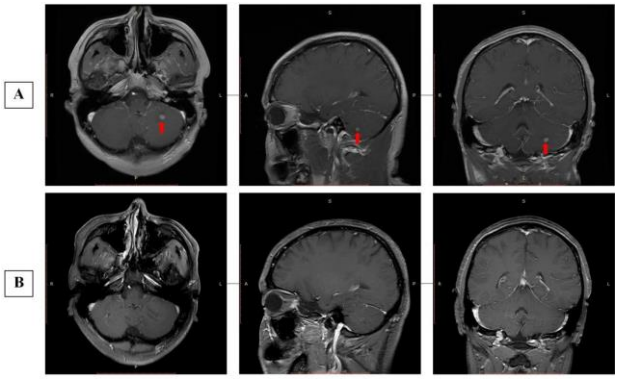

Figure 3: Radiological evaluation of intracranial oligometastasis. (A) Initial detection, (B) Five months after stereo tactic radio surgery.

Discussion

Based on NCCN guidelines, stage III NSCLC patients should receive multimodality therapies. Radical resection is recommended for operable patients. Potentially operable patients can gain opportunities for radical resection through neoadjuvant therapies including chemotherapy, radiotherapy, or a combination of both. Additionally, concurrent radical chemo radiotherapy followed by immunotherapy maintenance is preferred for inoperable patients. Notably, for locally advanced NSCLC patients with gene mutations, the NCCN guidelines do not indicate whether targeted therapy is superior to traditional chemotherapy as neoadjuvant or adjuvant treatment. This case report describes the application of neoadjuvant and adjuvant targeted therapy in a patient with stage IIIA-N2 ALK-positive NSCLC for the first time.

Crizotinib is an oral small-molecule TKI of ALK, MET, and ROS1 kinases and is a Category 1 recommendation for advanced ALK-positive NSCLC according to the NCCN guidelines since previous studies have demonstrated its superior efficacy over chemotherapy. In a profile 1014 study, crizotinib was associated with better Progression-Free Survival (PFS) compared to pemetrexed plus cisplatin or carboplatin chemotherapy in patients with advanced ALK-positive NSCLC (median, 10.9 months *vs.* 7.0months; P<0.001). A similar outcome was also observed in a profile 1029 study. Thus, the potential clinical benefits of targeted therapy adoption for ALK-positive locally advanced NSCLC should also be explored.

The CTONG 1103 trial explored erlotinib *vs.* gemcitabine plus cisplatin as neoadjuvant and adjuvant therapy in EGFR-positive stage IIIA-N2 NSCLC patients and showed that erlotinib significantly prolonged PFS (median, 21.5 months *vs.* 11.4 months; P<0.001). However, whether ALK-positive patients can also adopt this strategy remains unknown. In this case, the patient was not sensitive to first-line chemotherapy with gemcitabine plus cisplatin and was therefore switched to crizotinib based on his gene mutations, which enabled radical surgery. Kaoru Kaseda et al. and colleagues reported the first case of crizotinib application before surgical resection in ALK-positive NSCLC and showed promising disease reduction. Delphine Dumont et al and colleagues explored crizotinib as a second-line neoadjuvant treatment when chemotherapy failed to achieve

satisfactory regressionofthe tumor burden and observed no disease recurrence at 18 months post-surgery. In the present case, unlike the studies of Kaoru Kaseda and Delphine Dumont, a long-term follow-up of 61 months was performed.

Previous studies have demonstrated that stage N2 NSCLC patients benefit from PORT. However, in the CTONG 1103 trial PORT was not administered. Nevertheless, PORT was adopted for this patient. In terms of adjuvant targeted therapy, earlier trials explored the application of oral TKIs for EGFR-positive NSCLC patients, and the results were encouraging. ADJUVANT is the first prospective study comparing gefitinib with vinorelbine plus cisplatin as adjuvant treatments in patients with EGFR-positive stage II-IIIA (N1-N2) NSCLC, which showed that gefitinib significantly prolongs PFS (median, 28.7 months *vs.* 18.0 months; P=0.0054). The EVAN study explored erlotinib *vs.* vinorelbine plus cisplatin as adjuvant treatments in patients with EGFR-positive stage IIIA NSCLC and demonstrated substantially higher 2-year PFS rates of 81.2% in the erlotinib group and 44.6% in the chemotherapy group with oral TKI administration (P<0.001), reflecting the reliability of adopting oral TKIs as adjuvant treatment for certain groups. No relevant study has described ALK-positive NSCLC patients in this setting. Ultimately, the patient was given adjuvant crizotinib targeted therapy and has achieved considerable efficacy in terms of both PFS and OS, with a PFS 1 of 39 months and an OS of 61 months thus far. Notably, clinical stage IIIB NSCLC is associated with a poor survival outcome, with a median survival time of approximately 14.1 months which is substantially shorter than the PFS 1 of 39 months in this case.

To date, this is the first case of stage IIIA-N2 ALK-positive NSCLC treated with neoadjuvant and adjuvant targeted therapy combined with surgery and PORT to show remarkable clinical efficacy. Further exploration of this treatment model for stage III ALK-positive NSCLC is urgently needed.

Acknowledgments

This report was supported by grants from the State Key Laboratory of Respiratory Disease. The open project [grant number: SKLRD- OP-2018011], the State Key Laboratory of Respiratory Disease. The Independent project [grant number: SKLRD-QN-201720], Wu Jieping Fund-Ministry of Health Project [grant number: 320.6750.18125], Guangdong High Level University Clinical Cultivation Project [grant number: 2017-21020].

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