Case Report

Different Therapeutic Strategies in 2 Young Patients with Advanced ALK-Rearranged Lung Adenocarcinoma: “The Light at the End of the Tunnel”

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Keywords
Lung adenocarcinoma · Malignant pleural effusion · Anaplastic lymphoma kinase inhibitor therapy

Abstract
Malignant pleural effusion represents a prognostic negative factor on survival conferring stage IV disease. The median of survival is 5 months and a 5-year survival of about 3%. We describe the therapeutic success obtained from different strategies in anaplastic lymphoma kinase (ALK) inhibitors in 2 young women showing malignant pleural effusion secondary to advanced ALK-rearranged lung adenocarcinoma. This report shows that for patients with EGFR mutations in advanced lung adenocarcinoma-associated malignant pleural effusion, complete response to EGFR TKI inhibitor can be observed mostly if pleural effusion and primary lung adenocarcinoma show the same EGFR mutation status.
Introduction

Malignant pleural effusion can occur in patients with lung cancer, especially adenocarcinoma, and is often associated with poor prognosis [1]. At the time of diagnosis, most lung cancers are at advanced stage, at which the 5-year survival rate is only 5% [2]. In the last decade, innovative drugs acting against oncogenic drivers have dramatically improved prognosis identifying genotype-based target therapy as the main standard approach compared to histology-based systemic chemotherapy.

The rearrangements of the anaplastic lymphoma kinase (ALK) gene are present in 3–5% of non-small lung cancers, which is a subgroup of younger, never or light smoker patients which represents a hallmark of the adenocarcinoma histologic pattern [3]. Crizotinib, brigatinib, and alectinib represent the first- and second-generation ALK inhibitors showing efficacy superior to the existing platinum-based double-agent chemotherapy with significantly longer progression-free survival [3, 4].

The second-generation ALK inhibitors have been developed to overcome crizotinib resistance showing remarkable results as the standard first-line therapy for advanced ALK-positive lung cancer [5]. We describe the therapeutic success obtained from different strategies in ALK inhibitors in 2 young women with advanced lung adenocarcinoma-associated malignant pleural effusion.

Case Report

Case 1

In September 2014, a 28-year-old nonsmoking female was admitted to the hospital complaining of dyspnea and left chest pain. On chest CT scan, left massive pulmonary effusion with omolateral pulmonary atelectasis was observed (Fig. 1a). A pleural drainage was placed with immediate symptomatic relief, and cytological pleural fluid revealed metastatic adenocarcinoma.

The follow-up CT scan showed a left hilar tumor mass narrowing the left main bronchus associated with bilateral mediastinal and multiple systemic lymph nodes. A positron emission tomography-computed tomography confirmed the diagnosis of clinical stage IVB (T2b N3 M1c, TNM, version 8.0) (Fig. 1b). Definitive diagnosis of ALK-rearranged lung adenocarcinoma was obtained by bronchial biopsy of the tumor narrowing the left main bronchus (Fig. 1c).

Pemetrexed plus cisplatin (500 mg per square meter of body-surface area and 75 mg per square meter of body-surface area, respectively) was used every 3 weeks for up to 4 cycles,
and successively oral crizotinib at a dose of 250 mg twice daily was given for a year. Although noticeable response was obtained, the delayed side effects including diarrhea, nausea, and constipation resulted in discontinuation of treatment within 10–12 months. Crizotinib was shifted to brigatinib (at a dose 180 mg daily), and improvement of disease was observed on CT scan after 1 year achieving a durable complete response after 2 years until today (Fig. 1d, e).

**Case 2**

In March 2019, a 25-year-old nonsmoking female was admitted to the hospital complaining of cough and severe dyspnea. A chest CT scan showed right pleural effusion with bottom pleural thickening and subtotal atelectasis of the right lung associated with multiple mediastinal nodal involvement (Fig. 2a). Transthoracic ultrasound and medical pleuroscopy findings were mirror-like to chest CT scan imaging (Fig. 2b, c).

Exudative citrine yellow fluid was drained by ultrasound-guided thoracentesis, and diagnosis of ALK-rearranged lung adenocarcinoma was obtained on pleural fluid and confirmed on pleuroscopic pleural biopsies (Fig. 2d). Total body positron emission tomography with 18FDG confirmed a clinical stage IVA (cT3N2M1a, TNM version 8.0).

The chemotherapy with alectinib at 300 mg twice daily was performed, and the respiratory symptoms disappeared within 3 weeks. In 3 months, chest CT scan showed dramatic improvement of primary tumor with complete remission 15 months later (Fig. 2e).

**Discussion**

One of the problems that makes you lose sleep is to decide which treatment may prove efficacious for patients with non-small lung cancer. Over the last decade, the discovery of ALK rearrangements as an oncogenic molecular anomaly solved this “dilemma,” replacing standard chemotherapy with targeted therapies in specific molecular subgroup population with impressive improvements in survival.

Molecular genotyping is now routinely used to guide clinical care of lung adenocarcinoma patients, largely due to clinical trials that demonstrated superior efficacy of targeted kinase inhibitor compared to standard chemotherapy with impressive improvements in survival [6]. ALK rearrangements are observed in 2–7% of nonsmoking young patients with a solid-pattern dominant adenocarcinoma histology of which >50% have evidence of advanced disease [7].

Malignant pleural effusion appears in 15% of lung cancer patients, and the adenocarcinoma histotype is more frequently observed at the time of diagnosis [1]. The median survival...
in patients with malignant pleural effusion is about 5.5 months than 7.5 months for those without pleural effusion [1]. Crizotinib, brigatinib, and alectinib represent the first- and second-generation ALK inhibition drugs that have restored hope in patients with ALK+ advanced stage NSCLC.

In the first case, a sequential therapeutic strategy was performed according to later ALK inhibitor drug development. As reported in the literature, platinum-based chemotherapy was replaced with crizotinib which was significantly superior to standard chemotherapy in terms of clinical and radiological response [3].

In spite of significant improvement achieved with crizotinib, the side effects of crizotinib were overcome through the excellent tolerability shown by brigatinib. In this case, the therapeutic success of brigatinib as sequential strategy therapy was shown. In the second case, the dramatic response to alectinib as the first-line therapy validated the shift to second-generation ALK inhibitor to be the best approach in young patients with ALK+ advanced non-small lung cancer.

**Conclusion**

We describe the therapeutic success using different generations of ALK inhibitors in 2 young women with advanced lung adenocarcinoma-associated malignant pleural effusion. Perhaps, if concordance EGFR mutation status is observed, malignant pleural effusion does not influence the therapeutic success of second-generation ALK inhibitors: “the light at the end of the tunnel.”

**Statement of Ethics**

The procedures performed and described in this article were carried out in accordance with international guidelines and in accordance with the ethical standards of the Institutional Research Committee and the 1964 Declaration of Helsinki and its later amendment. The manuscript did not require ethics committee approval. Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

**Conflict of Interest Statement**

All authors involved in this work, U.C., C.C., E.Z., F.C., P.A., R.L., P.I., D.C., and D.A., declare no conflicts of interest with this manuscript.

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**Author Contributions**

U.C., C.C., E.Z., F.C., P.A., R.L., P.I., D.C., and D.A. were personally involved in the case reported. U.C., C.C., E.Z., F.C., P.A., R.L., P.I., D.C., and D.A. contributed to data collection and manuscript revision. U.C., C.C., E.Z., F.C., P.A., R.L., P.I., D.C., and D.A. contributed to study design, interpretation,
and manuscript revision. U.C., C.C., E.Z., F.C., P.A., R.L., P.I., D.C., and D.A. had full access to all the data in the work and take responsibility for data integrity, collection, accuracy, and description. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work. All authors involved in this work, U.C., C.C., E.Z., F.C., P.A., R.L., P.I., D.C., and D.A., declare that the manuscript, including related data, figures, and tables, has not been published previously and is not under consideration elsewhere.

**Data Availability Statement**

All data generated during this study are included in this article and can be enquired to the corresponding author.

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