Fishing for Precision in ALK-Rearranged Non-Small-Cell Lung Cancers

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Abstract

Fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC) represent the current standard for identification of therapeutically relevant anaplastic lymphoma kinase (ALK) rearrangements in advanced non-small-cell lung cancers (NSCLCs). Use of tyrosine kinase inhibitors (TKIs) targeting the oncogenic ALK fusion protein is approved for use in advanced ALK-rearranged NSCLCs and with benefits both with regards to clinical outcomes and quality of life when compared with traditional palliative cytotoxic therapies. We report here 2 cases in which initial standard of care ALK testing by FISH yielded false positive results, leading to delays in determination of optimal systemic therapy.

Keywords: Non-small cell lung cancer; NSCLC; ALK; Crizotinib; FISH; Targeted therapy

Introduction

Roughly 3-7% of non-small-cell lung cancers (NSCLCs) harbor anaplastic lymphoma kinase (ALK) rearrangements that are responsive to the tyrosine kinase inhibitor (TKI) crizotinib. Since August 2011, the Vysis ALK break apart FISH probe (Abbott Molecular, Inc.), had been the sole United States (US) Food and Drug Administration (FDA)-approved method for detection of ALK rearrangements in NSCLC, with the cutoff for ALK positivity defined as ≥15% of cells. However, as of June 2015, the VENTANA ALK (D5F3) CDx IHC assay (Ventana Medical Systems, Inc.) has been additionally approved. False negative and discordant ALK FISH results have been reported [1,2]. Here, we report patients who received false positive results on ALK FISH, leading to delay of optimal systemic therapy. ALK FISH testing in both instances was performed as a send out test by a certified commercial vendor utilizing the FDA-approved companion assay (Vysis ALK Break Apart FISH Kit, Abbott Molecular).

Case 1

An 83 year-old gentleman with a prior <10 pack/year tobacco history presented with metastatic lung adenocarcinoma (LAC) with malignant pleural effusion (Figure 1A). Single gene assays were completed on formalin-fixed, paraffin-embedded (FFPE) cell blocks created from the pleural fluid cytologic specimen and showed 16% of cells with an ALK rearrangement by FISH, EGFR, KRAS, and ROSI were unaffected. The patient was considered for a clinical trial (NCT02075840); however, central confirmation of tumor ALK status by IHC showed no evidence of an ALK rearrangement (IHC score was 0). Crizotinib 250 mg twice daily was started. Follow-up one month later demonstrated clinical and radiographic disease progression (Figure 1B). Right pleural biopsy and targeted next generation sequencing (SNaPshot NGS and fusion gene assay, Massachusetts General Hospital) demonstrated an EGFR exon 19 deletion, with no evidence of ALK gene fusion. Crizotinib was discontinued, and erlotinib at a dose of 150 mg daily was started. This resulted in a partial radiographic response with improvement in clinical symptoms that has been sustained for 6 months (Figure 1C).

Case 2

A 64 year-old woman with a prior 10 pack/year tobacco history presented with metastatic LAC with malignant pleural effusion (Figure 2A). Sequential single gene assays were completed on FFPE cell blocks created from the pleural fluid cytologic specimen. The tumor was found to harbor both ALK rearrangement by FISH in >90% of cells and concurrent EGFR exon 19 mutation. Crizotinib 250 mg twice daily was started. However, symptomatic and radiographic progression following six weeks of therapy was noted (Figure 2B). Repeat testing on the same cytologic specimen again showed an ALK rearrangement by FISH; however, NGS showed the EGFR exon 19 mutation only. Crizotinib was discontinued, and erlotinib 150 mg daily was started. Eight weeks later, imaging showed a partial response that has been sustained for more than 9 months (Figure 2C).

Discussion

With the dramatic responses and tolerability observed with the use of crizotinib in ALK-rearranged NSCLC, it has become imperative to perform timely and accurate molecular testing. Currently, both FISH and IHC serve as FDA-approved options for testing. Nevertheless, there have been an increasing number of reports highlighting false negative results using FISH, on the order of 5-15% [3]. False negative results

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Received: October 22, 2015; Accepted: December 03, 2015; Published: December 07, 2015

Citation: Le X, Peters ML, VanderLaan PA, Costa DB, Rangachari D (2015) Fishing for Precision in ALK-Rearranged Non-Small-Cell Lung Cancers. Oncol Cancer Case Rep 1:105. doi:10.4172/2471-8556.1000105

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may occur due to variant forms of EML4-ALK rearrangements and/or RNA editing abnormalities resulting in intron changes that cannot be detected by FISH [4]. Several groups have published on the comparative accuracy of FISH, IHC, and NGS; however, the sensitivity, specificity, and cost of these modalities have not been directly compared in large prospective trials to date [3-6]. We report here two cases with clinically false positive FISH results. In both cases, initiation of crizotinib resulted in rapid disease progression and warranted further interrogation by NGS. Interestingly, both tumors were found to harbor EGFR mutations and with brisk and ongoing responses to erlotinib. The practice of precision medicine is incumbent upon use of assays which detect drug targets with optimal accuracy. As NGS becomes increasingly accessible and cost effective and as the spectrum of actionable therapeutic targets continues to expand, NGS may replace other modalities for optimally pairing patients with best therapies especially in cases where there is a paradoxical/unexpected response to therapy that is inconsistent with the predictive biomarker assayed.

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