Case report: BRAF A598-T599insV mutation as a potential resistance mechanism to alectinib in ALK-rearranged lung adenocarcinoma

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Anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) have improved the prognosis of advanced-stage non-small cell lung cancer (NSCLC) with ALK rearrangement, but resistance mechanisms limit their efficacy. We describe the case of a 63-year-old man with a stage IVA ALK-rearranged lung adenocarcinoma who developed a BRAF A598-T599insV mutation as a potential resistance mechanism to alectinib, a second-generation ALK TKI. He was treated with an association of BRAF and MEK inhibitors but death occurred two months after treatment initiation in a context of tumor progression and toxicity. Based on this first report of BRAF A598-T599insV mutation occurring in lung cancer, we discuss resistance mechanisms to ALK TKIs, implications of BRAF mutation in NSCLC, and BRAF A598-T599insV mutation in other cancers.

KEYWORDS
ALK rearrangement, BRAF A598-T599insV mutation, lung adenocarcinoma, resistance to alectinib, non-small cell lung cancer
Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, responsible for 1.5 million deaths per year (1). There are two histological types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), representing ≃85% and ≃15% of cases respectively (2). NSCLC is further divided into three histological subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, representing ≃40-50%, ≃30%, and ≃10% of cases respectively. In NSCLC, oncogenic drivers such as EGFR, BRAF V600E, MET exon14, KRAS G12C mutations, and Anaplastic lymphoma kinase (ALK), ROS-1, RET, and NTRK rearrangements have been identified and led to personalized medicine after clinical trials showed that targeted therapies against these abnormalities improved outcomes as compared to chemotherapy (3, 4).

ALK rearrangement was discovered in NSCLC in 2007. It results from an interchromosomal inversion within chromosome 2’s short arm, leading to ALK’s 3’ end fusion with Echinoderm microtubule-associated protein-like-4 (EMLA1)’s 5’ end or, less frequently, another gene (e.g.: KIF5B, HIP1, TPR, BIRC6). The resulting protein is activated and leads to cancer development through the activation of downstream signaling pathways such as the mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT), and Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathways. ALK rearrangement, observed in 2-7% of NSCLCs, is more frequent in patients with adenocarcinoma, never/light-smoking history, and younger age (5, 6).

Crizotinib was the first ALK tyrosine kinase inhibitor (TKI) evaluated in ALK-rearranged NSCLC. Randomized trials showed that overall response rate (ORR) and progression-free survival (PFS) were better with crizotinib than chemotherapy in first- and further-line treatment of advanced-stage ALK-rearranged NSCLC. However, resistance mechanisms occur inevitably, responsible for tumor progression. Second-generation (alectinib, ceritinib, brigatinib, and ensartinib) and third-generation (lorlatinib) ALK TKIs have therefore been developed, but also face resistance issues. ALK-dependent resistance mechanisms consist mainly of mutations in ALK tyrosine kinase domain (altering kinase conformation and/or ATP binding affinity and preventing TKI binding) and less frequently of ALK amplification. ALK-independent mechanisms include bypass and downstream signaling activation (6–11).

In this report, we present a BRAF A598-T599insV mutation as a new potential ALK-independent resistance mechanism to alectinib in a patient with metastatic ALK-rearranged lung adenocarcinoma. We also discuss literature related to resistance to ALK TKIs, BRAF mutation in NSCLC, and BRAF A598-T599insV mutation in other cancers.

Case presentation

In 2016, a 63-year-old never-smoking male patient, with a history of resected prostatic adenocarcinoma in 2006, was diagnosed with a left lower lobe lung adenocarcinoma, stage cT1A (UICC 7th edition) (cT2a cN3 cM1a (metastases in the contralateral lung)). While there was no oncogenic driver found by a DNA Next Generation Sequencing (NGS) panel (Ion Torrent, ThermoFisher) targeting 22 genes (Supplementary Table 1), further molecular analyses revealed an ALK rearrangement (score 2+ ALK expression by immunohistochemistry, confirmation by fluorescent in situ hybridization (FISH) (38% of analyzed tumor cells were positive) and by RNA NGS (11.115 reads), which revealed an Echinoderm microtubule-associated protein-like 4 (EMLA1) (12)-ALK (12) fusion (Figure 1).

In 2016 in Belgium, ALK TKIs were not reimbursed in first-line and so, the patient initially received cisplatin-pemetrexed chemotherapy, with partial tumor response observed after three (Figures 2A, B) and five cycles. Then, pemetrexed maintenance was initiated but stopped after seven cycles despite stable disease because of a grade 2 asthenia and a grade 1 renal failure. He experienced tumor progression 2.5 months after stopping pemetrexed (Figure 2C).

Crizotinib was initiated in second-line, with partial response achieved after two months (Figure 2D) and disease progression observed in the left lung after 5.5 months (Figure 2E). Tumor biopsies showed persistence of an ALK rearrangement (30% of analyzed tumor cells positive by FISH and 15.431 reads by RNA NGS) but no resistance mechanism to crizotinib (screening with a DNA NGS panel (Ion Torrent, ThermoFisher) targeting 22 genes, including ALK exons 22, 23, and 25).

In third-line, the patient received alectinib. Partial response was observed after two months (Figure 2F), followed by stabilization until tumor progression after 15 months (increase of the lesions in the left lower lobe and occurrence of a left 

Abbreviations: AKT, protein kinase B; ALK, anaplastic lymphoma kinase; BIRC6, Baculoviral IAP Repeat Containing 6; BRAF, v-raf murine sarcoma viral oncogene homolog B1; EGFR, epidermal growth factor receptor; EMLA4, echinoderm microtubule-associated protein-like; FISH, fluorescent in situ hybridization; HIP1, Huntingtin Interacting Protein 1; JAK, Janus kinase; KIF5B, Kinesin Family Member 5B; KRAS, Kirsten rat sarcoma viral oncogene homolog; MAPK, mitogen-activated protein kinase; MEK, Mitogen-Activated Protein Kinase Kinase 1; MET, hepatocyte growth factor receptor; NGS, Next Generation Sequencing; NSCLC, non-small cell lung cancer; NTRK, neurotrophic receptor tyrosine kinase; ORR, overall response rate; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; RET, rearranged during transfection; ROS-1, c-Ros oncogene 1; SCLC, small cell lung cancer; STAT, signal transducer and activator of transcription; TKI, tyrosine kinase inhibitor; TPR, Translocated Promoter Region, Nuclear Basket Protein.
pleural carcinomatosis) (Figure 2G). Tumor re-biopsies revealed persistence of an ALK rearrangement (24% of analyzed tumor cells positive by FISH and 16.286 reads by RNA NGS) and detected a BRAF A598_T599insV mutation (allelic frequency of 11%, screening with a DNA NGS panel (Ion Torrent, ThermoFisher) targeting 25 genes [the same 22 genes than in the panels used at diagnosis and at progression on crizotinib, plus three other genes (Supplementary Table 2)], while there was no ALK mutation.

Therefore, we did not propose a third-generation ALK TKI in fourth-line but an experimental treatment associating BRAF and MEK kinase inhibitors. Unfortunately, the patient died two months later in a context of tumor progression (Figure 2H) and toxicity (grade 3 skin rash and amylase elevation). The timeline of patient clinical history, with tumor evolution and treatments, is represented in Figure 3.

Discussion

We report here the BRAF A598_T599insV mutation as a potential new resistance mechanism to alectinib in metastatic ALK-rearranged lung adenocarcinoma.

After platinum-based chemotherapy, the patient was treated with crizotinib. Progression under crizotinib was observed after only 5.5 months and re-biopsies did not reveal any molecular resistance mechanism. Resistance to crizotinib is usually acquired (93-95%) and secondary to ALK-dependent or, more frequently, ALK-independent mechanisms (2/3 cases) (7). ALK-dependent resistance mechanisms include ALK mutations (the most frequent ones being L1196M (7%) and G1269A (4%), the less frequent ones C1156Y/T, L1152P/R, I1151Tins, F1174C/L/V, G1128A), ALK amplification (7-18%), and loss of ALK rearrangement (8, 11). ALK-independent resistance mechanisms include activation of bypass signaling pathways (e.g.: EGFR mutation and/or amplification, KRAS mutation, KIT amplification, IGF-1R activation, RAS/MEK activation), histological transformation to SCLC, and epithelial to mesenchymal transition (EMT) (11).

To overcome these resistance mechanisms to crizotinib, second-generation ALK TKIs have been developed. Randomized trials demonstrated their superiority over chemotherapy after progression on crizotinib, even in the absence of ALK mutations, which occur only in a minority of cases (~20%) in this setting (7). Patients progressing on crizotinib generally remain ALK-dependent despite the absence of ALK mutations probably because of the low potency of crizotinib against ALK. However, it is possible that sequencing panels do not adequately capture low frequency variants or previously undescribed ALK resistance mutations. In this context of tumor progression on crizotinib and absence of a specific resistance mechanism, our patient was treated with second-generation alectinib. Progression was observed after 15 months. ALK-dependent resistance mechanisms are more frequent with second-generation (1/2 cases) than first-generation TKIs and seem to increase with each successive generation of ALK TKI. The most frequent ALK mutation of resistance to second-generation TKIs is G1202R (21% post-ceritinib, 29% post-alectinib, and 43% post-brigatinib). Less frequent secondary ALK mutations are F1174C/L (17%), I1156Y (8%), G1202del (8%) post-ceritinib, I1171T/S (12%), V1180L (6%), and L1196M (6%) post-alectinib, and E1210K (29%), D1203N (14%), S1206Y/C (14%) post-brigatinib (11). ALK-independent resistance mechanisms to second-generation ALK TKIs include alterations in bypass activating pathways (such as RET fusion, MET amplification, mutation, or rearrangement, PIK3CA, FGRFR2, MEK, and NRAS mutations), SCLC transformation, and EMT (11). Similarly,

![FIGURE 1](Pasau et al. 10.3389/fonc.2022.985446)
FIGURE 2
Chest imaging evolution. (A) Computed tomography (CT) at diagnosis: presence of a left-lower lobe primary tumor (red arrow). (B) CT after three cycles of cisplatin and pemetrexed in first-line: partial tumor response with decreased size of the primary tumor (red arrow). (C) CT after 7 cycles of pemetrexed in maintenance and then 2.5 months without systemic treatment: tumor progression with increased size of the primary tumor (red arrow). (D) CT after two months on crizotinib in second-line: partial tumor response with decreased size of the primary tumor (red arrow). (E) CT after 5.5 months on crizotinib in second-line: progression of the primary tumor (red arrow), appearance of ground glass opacities (blue arrow), a retro-obstructive condensation in the left lower lobe (red cross), and a nodular lesion in the lingula (green arrow). (F) CT after two months on alectinib in third-line: partial tumor response with decreased size of the left lower lobe primary tumor (red arrow) and of the lingular nodule (green arrow). (G) CT after 15 months on alectinib: tumor progression with increased size of the primary tumor (red arrow) and appearance of a left pleural effusion (area under red dots). (H) Radiography after two months on BRAF/MEK inhibitors in fourth-line: left pleural effusion (area under red dots).
third-generation TKI lorlatinib has been developed to overcome these resistance mechanisms to second-generation ALK TKIs. In a phase 2 trial with lorlatinib, analysis of plasma and tissues from 198 ALK-rearranged NSCLC patients showed that those with ALK mutations post-second-generation TKI had higher ORR than those without (62% vs 32% in plasma and 69% vs 27% in tissue) (13). While ALK-independent resistance mechanisms remain sensitive to ALK inhibition post-crizotinib due to crizotinib’s lower potency, this is no longer the case post-second/third-generation TKI’s (11).

In our patient, in the absence of an ALK mutation but presence of a BRAF A598_T599insV mutation at progression on alectinib, we proposed participation in a phase 1b clinical trial evaluating a BRAF and a MEK inhibitor in BRAF- and KRAS-mutated NSCLC and NRAS-mutated melanoma instead of a treatment with lorlatinib.

BRAF mutations are found in 1.5-3.5% of NSCLCs at diagnosis, almost exclusively in adenocarcinoma, and are responsible for the MAPK/ERK pathway activation leading to tumor development and progression (14). Half of BRAF-mutated NSCLCs have a BRAF V600E mutation, which is more frequent in light/never-smokers and, at diagnosis, is mutually exclusive with other oncogenic drivers such as ALK rearrangement. BRAF V600E-mutated NSCLC’s treatment consists of a BRAF inhibitor (vemurafenib or dabrafenib) in association with a MEK inhibitor (trametinib). The response to BRAF/MEK inhibitors in presence of BRAF non-V600E mutations is less consistent, some of them being sensitive to BRAF/MEK inhibitors (e.g.: BRAF L597 and K601 mutations), while others not (e.g.: BRAF G464 and G469 mutations) (15). BRAF mutations can also occur as an acquired resistance to other targeted therapies, and have only recently been reported as a resistance mechanism to ALK TKIs. BRAF G15V mutation was first observed in one among 27 NSCLC patients progressing on second-generation ALK TKI (3.7%) (7). BRAF mutations were then reported in circulating tumor cells of 3/14 patients progressing on crizotinib (D587A in one, E586K and I592M in a second, and E586K in a third patient) (10). BRAF V600E mutation was observed in a patient with ALK-rearranged lung adenocarcinoma previously treated with crizotinib and pemetrexed (16). Because BRAF and/or MEK inhibitors were not available, the patient was treated with alectinib, but experienced tumor progression after three months. At time of progression on alectinib, rebiopsies showed persistence of the BRAF V600E mutation. BRAF V600E mutation was also found, with an ALK I1171T mutation, in a patient with ALK-rearranged lung adenocarcinoma progressing on alectinib after crizotinib (17). The patient died three months after lorlatinib was initiated. Finally, BRAF V600E mutation was found in a patient-derived xenograft (PDX) model from a patient progressing on alectinib (18). Triple combination of alectinib, dabrafenib, and trametinib effectively and safely suppressed tumor growth in this PDX model. To the best of our knowledge, the BRAF A598_T599insV mutation has never been described in lung cancer before, while only once in papillary thyroid carcinoma (19) and twice in melanoma (12, 20). Due to the rarity of non-V600E BRAF mutations in cancer, their clinical significance remains to be established. In this rare subset of non-V600E BRAF mutations in cancer, their clinical significance remains to be established. In this rare subset of non-V600E BRAF mutations in cancer, their clinical significance remains to be established. In this rare subset of non-V600E BRAF mutations in cancer, their clinical significance remains to be established.

FIGURE 3
Timeline graph of patient clinical history, with tumor evolution and treatments. P, tumor progression; PR, tumor partial response; SD, tumor stable disease; TKI, tyrosine kinase inhibitor.
may be explained by the fact that the ALK rearrangement was still present in the tumor biopsies obtained at progression on alectinib, in addition to the BRAF A598-T599insV mutation, these two genetic abnormalities activating different signaling pathways leading to tumor progression. Therefore, as BRAF and MEK inhibitors do not inhibit ALK and all its downstream signaling pathways, cells with ALK rearrangement were probably not controlled by the BRAF/MEK inhibitors targeting only the BRAF-mutated cells. This is often an issue in the context of acquired resistance mechanisms to oncogenic drivers, encouraging the association of multiple targeted therapies, as previously reported for instance in presence of an EGFR mutation and a BRAF V600 mutation as resistance mechanism to the third-generation EGFR TKI osimertinib (21). Even though this kind of association is interesting from a theoretical point of view, toxicity may be a problem and is the reason why we did not consider it in our patient and preferred to propose him participation in a clinical trial. In the absence of response to BRAF/MEK inhibitors, it is difficult to confirm that this BRAF A598-T599insV mutation was a resistance mechanism to alectinib in our patient. It is indeed possible that the BRAF mutation was the selection of a preexisting BRAF-clone by alectinib, even though not identified before.

Conclusion

In a patient with ALK-rearranged lung adenocarcinoma progressing on alectinib, we detected a BRAF A598-T599insV mutation, suggesting it as a resistance mechanism to alectinib. To our best knowledge, the BRAF A598-T599insV mutation has never been described before in lung cancer. Further research is needed to determine whether this mutation is a resistance mechanism to alectinib in lung cancer and what is the best treatment in this setting.

Data availability statement

The datasets for this article are not publicly available due to concerns regarding participant/patient anonymity. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

This study was reviewed and approved by Ethical Committee of CHU UCL Namur (Godinne Site). Written informed consent was not provided because the patient deceased before the writing of the manuscript and the family has not been contacted to avoid painful memories. Ethical Committee of CHU UCL Namur provided the authorization to publish this case report without written informed consent.
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