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Case Report

BRAF Mutations in Lung Cancer: When Looking for the Needle in the Haystack

Zatarain-Barrón ZL[1], Cardona AF[2,3]*, Barrón F[1], Rojas L[2-4] and Arrieta O[1]

[1]Thoracic Oncology Unit, Instituto Nacional de Cancerología (INCan), México City, México

[2]Clinical and Traslational Oncology Group, Clínica del Country, Bogotá, Colombia

[3]Foundation for Clinical and Applied Cancer Research - FICMAC, Bogotá, Colombia

[4]Department of Oncology, Clínica Colsanitas, Bogotá, Colombia

***Corresponding author:** Cardona AF, Clinical and Translational Oncology Group, Institute of Oncology, Clínica del Country, Bogotá, Colombia/Foundation for Clinical and Applied Cancer Research (FICMAC), Bogotá, Colombia

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Introduction

The BRAF gene on chromosome 7 (7q34) encodes a Ser-Thr protein kinase that belongs to the highly oncogenic RAS/RAF/MEK/ERK signaling pathway, a direct effector of RAS, which induces its activation by dimerization, and thereafter activates MAP kinase/ERK signaling pathway [1]. Downstream of ERK are mainly cytoplasmic proteins and transcription factors that promote cell survival, proliferation, and motility while inhibiting differentiation. Recently, non-coding effectors such as microRNAs and long non-coding RNAs have also been discovered [1,2]. Additionally, an increase in protein expression can disturb the Ras-MAPK signaling pathway, which in turn can result in different developmental disorders such as Noonan syndrome, cardiofaciocutaneous syndrome, Costello syndrome, and different types of human cancers [3-5].

In addition to germline mutations, BRAF somatic mutations have been reported in about 7% of all cancers, including 100% of Hairy Cell Leukemia (HCL) cases, 50-60% of melanomas, 30-50% of papillary thyroid carcinomas, 10-20% of colorectal cancers, and 3-5% of non-small cell lung cancers [6,7].

More than 40 different mutations have been identified in the BRAF gene in human cancer. Ninety percent of BRAF mutations are accounted for by a thymine to adenine single-base change at position 1,799. This missense mutation, located in exon 15, results in a change at residue 600 that substitutes glutamine for valine (V600E) [7]. In addition, the amino acid variations observed as a result of BRAF mutations are mostly clustered in two regions: the glycine rich P loop region and the activation domain-protein kinase domain [8]. These mutations change the activation peptide from an active state to an inactive state. For instance, the charge density of the phenyl ring of Phe467 in the P loop interacts with the aliphatic side chain of vicinal Val600. However, in the case of substitution of the medium-sized hydrophobic Val with a bulky charged moiety (Glu, Asp, Lys, or Arg), as is often found in human cancers, the interactions that preserve the DFG motif in an inactive conformation are destabilized, hence, the activation segment flips stereo chemically into an inactive position [8,9]. Depending on the nature of the mutation, the activity of the BRAF protein downstream varies, thereby resulting in the stimulation of several pathways.

Recently, Cui et al., performed a systematic review which included 11,711 patients with Non-Small Cell Lung Cancer (NSCLC). Interestingly, the authors found an overall BRAF mutation rate of 2.6% (303/11,711), and this condition was significantly associated with adenocarcinomas (OR=3.96, 95% CI=2.13-7.34), female gender (OR=0.72, 95% CI=0.55-0.95) and never smokers (OR=0.12, 95% CI=0.05-0.29). Preclinical data in mice suggested a potential oncogenic role of BRAF mutations in the development of lung adenocarcinoma, however, half of BRAF mutations are non-V600E, and these mutations often occur in the phosphate-binding loop (P-loop) at G466 and G469 [10]. While BRAFV600E mutant demonstrates several hundred folds elevation of BRAF kinase activity over wild-type BRAF, the biochemistry of BRAFnon-V600E proteins varies substantially. Some of the BRAFnon-V600E mutant proteins such as BRAFG469A and BRAFL597V, confer increased kinase activity, this can result in the mutated proteins being 266 times and 64 times more active compared to wild-type BRAF, respectively [8,11]. BRAFnon-V600E mutants with elevated kinase activity were shown to function as constitutive RAS-independent dimmers. In contrast, other non-V600E mutants, such as BRAFG466V and BRAFD594G, have impaired BRAF kinase activity compared to wild-type BRAF; however, these kinase-impaired BRAF proteins can still activate the MAPK pathway via alternative routes that rely on its heterodimerization with CRAF [11]. Since both classes of BRAFnon-V600E mutant proteins enhance MAPK signaling, MEK inhibition has been assessed in these cancers, demonstrating growth inhibition in BRAFnon-V600E mutant lung cancer cell lines *in vitro* [12].

The biological and prognostic impact of BRAF mutations in NSCLC have been reported in several retrospective studies, all limited by small patient numbers [13,14]. Paik et al., found no difference in Overall Survival (OS) for BRAF-mutated patients when compared with other EGFR mutated, ALK-mutated, or KRAS-mutated subpopulations [15]. On the other hand, Marchetti et al., described that patients with the BRAF V600E mutation had shorter Disease-Free Survival (DFS) and OS compared with wild-type and non-V600E mutations, particularly those related with an aggressive micro papillary subtype [16]. Together, this information and profiling allowed the initiation of studies with tyrosine kinase inhibitors; *in vitro*

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preclinical models of NSCLC demonstrated that both vemurafenib and trametinib were effective as single agents in BRAF V600E mutant cells [17]. Moreover, trametinib was also effective in non-V600E mutants. The combination of vemurafenib and trametinib increased tumor cell death, suggesting that the combination should be more effective. Two other MEK inhibitors (PD0325901 and CI-1040) have also shown activity in *in vitro* and *in vivo* preclinical models of NSCLC with BRAF V600E or non-V600E mutations [17,18].

In patients with NSCLC harboring the BRAF V600E mutation, Partial Responses (PR) or Complete Responses (CR) have been reported for vemurafeniband and dabrafenib monotherapy, however, these were not durable [14]. Previously, the EURAF multicenter study collected data from patients with advanced NSCLC with BRAF mutations, who were treated with at least one BRAF inhibitor in regular clinical practice. Out of 35 patients (all with adenocarcinoma), 83% had BRAF V600E mutations, and 17% had non-V600E mutations (such as G466V, G469A, G469L, G596V, V600K, and K601E). Seventy-four percent of patients received vemurafenib, 23% dabrafenib, and 3% sorafenib. Most patients received one line of BRAF inhibitors, whereas 11% of patients received two lines. Although most BRAF inhibitors (86%) were used after at least one line of chemotherapy, five patients received BRAF inhibitors as first line, and among these three achieved a PR. Overall Response Rate (ORR) was 53%, with 85% Disease Control Rate (DCR), including 6% CR, 47% PR, and 32% stable disease [18]. The planned subgroup analysis of BRAF V600E patients receiving vemurafenib showed 54% ORR and 96% DCR. PFS with first-line therapy (including chemotherapy) was 9.3 months for V600E and 1.5 months for non-V600E, and OS was 25.2 and 11.8 months, respectively. Overall, PFS and OS using a BRAF inhibitor for V600E mutants were 5 and 10.8 months, respectively. The duration of BRAF therapy was 4.3 months, ranging from 0.5 to 41 months, with some patients having long lasting responses. Most cases with non-V600E mutations did not respond to BRAF inhibitors and had a significantly poorer outcome, although a CR was observed in one BRAF G596V-mutated NSCLC patient treated with vemurafenib. Until now, the mechanism of non-V600E BRAF-mutated NSCLC primary resistance to BRAF inhibitors is not fully understood. Three-dimension structural modeling of BRAF G469L suggested that it induces a conformational change impairing the binding of vemurafenib and dabrafenib [19].

Recently, Planchard et al., published the results of a phase II trial that included 36 patients treated with first-line dabrafenib plus trametinib. Median follow-up was 15.9 months and the proportion of patients with ORR was 23 (64%, 95% CI 46-79), with two (6%) cases achieving a CR and 21 (58%) a PR. All cases presented one or more Adverse Event (AE) of any grade, and 25 (69%) had one or more grade 3 or 4 event. The most common grade 3 or 4 AEs were pyrexia (11%), alanine aminotransferase increase (11%), hypertension (11%), and vomiting (8%). These results brought about the recognition of a new paradigm therapy with clinically meaningful antitumor activity and a manageable safety profile in patients with previously untreated BRAFV600E-mutant NSCLC [20].

We will wait with some anxiety for mature results of the novel BRAF inhibitor LGX818 that is currently being evaluated as monotherapy in an open-label, multicenter, single-arm phase II study in BRAF V600-mutated advanced NSCLC (NCT02109653). LGX818 is also being evaluated either in combination with the MEK inhibitor MEK162 or as a triple combination with MEK162 and the cyclin-dependent kinase inhibitor LEE011 in an open-label, multicenter, phase Ib/II study in BRAF-mutated advanced solid tumors (NCT01543698). Other interesting ongoing studies are the phase Ib/II studies assessing the Phosphatidylinositol 3-kinase (PI3K) inhibitor BKM120 either in combination with trametinib (NCT01155453) or the MEK inhibitor MEK162 (NCT01363232) in selected advanced solid tumors, including BRAF-mutated NSCLC. The MEK inhibitor selumetinib is also being assessed in a phase II study in non-melanoma tumors with BRAF mutations (NCT00888134). With the emergence of immunotherapy, a combining BRAF and/or MEK inhibitors and immunotherapy is currently ongoing. Interestingly, Li et al., reported the case of a 74-year-old woman treated sequentially with dabrafenib and pembrolizumab, interventions with which she achieved a prolonged survival [21].

The mass amount of information regarding NSCLC made available through the increasing use of genotyping technology has made it possible to find a needle in a haystack. The presence of BRAF mutations corresponds to a therapeutic target potentially modularly with targeted therapy alone or in combination.

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