EGFR Inhibitors Plus Bevacizumab are Superior Than EGFR Inhibitors Alone as First-Line Setting in Advanced NSCLC With EGFR Mutations and BIM Deletion Polymorphisms (BIM-CLICaP)

Los inhibidores de EGFR más bevacizumab son superiores a los inhibidores de EGFR solos como configuración de primera línea en NSCLC avanzado con mutaciones de EGFR y polimorfismos de deleción BIM (BIM-CLICaP)

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ABSTRACTO: Purpose: BIM activation is essential for epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI)-triggered apoptosis in EGFR-mutant non-small-cell lung cancer (NSCLC). A deletion in the intron two of the BIM gene results in generation of alternatively spliced isoforms that impairs their apoptotic response to TKIs, conferring the NSCLC cells intrinsic resistance to these medications. Patients with both alterations have poor clinical evolution. The current study aimed to investigate the clinical efficacy and tolerability of EGFR-TKIs plus bevacizumab (Bev) versus EGFR-TKIs alone as first-line treatment in advanced NSCLC patients with EGFR mutations and BIM deletions (BIMdel). Materials and methods: A retrospective analysis was conducted. BIMdel was detected using polymerase chain reaction analysis and direct sequencing of DNA. BIM protein expression was investigated by immunohistochemistry, and BIM mRNA levels by reverse transcriptase-polymerase chain reaction. Clinical characteristics, overall survival, progression-free survival (PFS), overall response rate (ORR), and treatment-related adverse events were compared between both groups.Results: Thirty-three patients were included; 15 received EGFR-TKIs, and 18 received EGFR-TKIs plus Bev. The median age was 63 years, with a majority of recruited female patients. All included individuals had an Eastern Cooperative Oncology Group performance score of 2 or less. The addition of Bev resulted in a significantly higher ORR (94.4% v 40%, P > .001). Median PFS was longer with the use of the combination therapy (11.12 v 7.87 months; P = .001). Median overall survival tended to be longer in the EGFR-TKIs plus Bev (30.9 v 25.4 months; P = .06) but failed to reach statistical significance. Response in terms of both partial and complete as well as overall favorably affected PFS. Conclusion: EGFR-TKIs plus Bev conferred a significantly higher ORR and PFS in advanced NSCLC patients with EGFR mutation and BIMdel. Further prospective studies are needed to validate these findings.

STK11 and KEAP1 mutations in non-small cell lung cancer patients: Descriptive analysis and prognostic value among Hispanics (STRIKE registry-CLICaP)

Mutaciones STK11 y KEAP1 en pacientes con cáncer de pulmón de células no pequeñas: análisis descriptivo y valor pronóstico entre hispanos (registro STRIKE-CLICaP)

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ABSTRACTO: Background: Mutations in STK11 (STK11Mut) and, frequently co-occurring, KEAP1 mutations (KEAP1Mut) are associated with poor survival in metastatic Non-small Cell Lung Cancer (mNSCLC) patients treated with immunotherapy. However, there are limited data regarding the prognostic or predictive

significance of these genomic alterations among Hispanics. Methods: This retrospective study analyzed a cohort of Hispanic patients (N = 103) diagnosed with mNSCLC from the US and seven Latin American countries (LATAM) treated with immune checkpoint inhibitors (ICI) alone or in combination as first-line (Cohort A). All cases were treated in routine care between January 2016 and December 2021. The main objectives were to determine the association of mutations in STK11 or KEAP1 in these patients' tumors with overall (OS) and progression-free survival (PFS), presence of KRAS mutations, tumor mutational burden (TMB), and other relevant clinical variables. To compare outcomes with a STK11Wt/KEAP1Wt population, historical data from a cohort of Hispanic patients (N = 101) treated with first-line ICI was used, matching both groups by country of origin, gender, and Programed Death-ligand 1 (PD-L1) expression level (Cohort B). Results: Most tumors had mutations only in STK11 or KEAP1 (45.6%) without KRAS co-mutation or any other genomic alteration. Besides, 35%, 8.7%, 6.8%, and 3.9% were KRASMut + STK11Mut, KRASMut + STK11Mut + KEAP1Mut, STK11Mut + KEAP1Mut, and KRASMut + KEAP1Mut, respectively. Based on KRAS status, STK11 alterations were associated with significantly lower PD-L1 expression among those with KRASWt ($p = 0.023$), whereas KEAP1 mutations were predominantly associated with lower PD-L1 expression among KRASMut cases ($p = 0.047$). Tumors with KRASMut + KEAP1Mut had significantly higher median TMB when compared to other tumors ($p = 0.040$). For Cohort A, median PFS was 4.9 months (95%CI 4.3-5.4), slightly longer in those with KEAP1mut 6.1 months versus STK11Mut 4.7 months ($p = 0.38$). In the same cohort, PD-L1 expression and TMB did not influence PFS. OS was significantly longer among patients with tumors with PD-L1 ≥ 50% (30.9 months), and different from those with PD-L1 1-49% (22.0 months), and PD-L1 < 1% (12.0 months) ($p = 0.0001$). When we compared the cohorts A and B, OS was significantly shorter for patients carrying STK1 [STK11Mut 14.2 months versus STK11Wt 27.0 months ($p = 0.0001$)] or KEAP1 [KEAP1Mut 12.0 months versus KEAP1Wt 24.4 months ($p = 0.005$)] mutations. PD-L1 expression significantly affected OS independently of the presence of mutations in STK11, KEAP1, or KRAS. TMB-H favored better OS. Conclusions: This is the first large Hispanic cohort to study the impact of STK11 and KEAP1 mutations in NSCLC patient treated with ICI. Our data suggest that mutations in the above-mentioned genes are associated with PD-L1 expression levels and poor OS.