FGFR AMPLIFICATION AND EXPRESSION STATUS IN SQ-NSCLC

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Background

FGFR type 1 (FGFR1) gene amplification has been identified as one of the key potentially actionable targets in SQCLC, given FGFR1 role in oncogenesis and relatively high event frequency (~20% patients). Equivocal results from the pre-clinical and clinical studies point at the necessity of efficient and reliable predictive identification of potential candidates for therapy with FGFR1 inhibitors. Meanwhile, published data regarding correlation between FGFR1 protein expression and FGRF1 gene amplification are discordant. Our previous analyses demonstrated relatively low intra-tumor heterogeneity of both markers in retrospectively analyzed SQCLC series of 20 tumors but also implied their low conformity. Therefore, we aimed at verifying their concordance, or lack thereof, in the larger series of SQCLC tumors.

Methods

74 SQCLC tumors were analyzed (2 FFPE sections per tumor). FGFR1 gene copy number was assessed by FISH method using probes specific for the 8p12 locus and the chromosome 8 centromere (CEN8). Criteria of FGFR1 amplification were as follows: FGFR1/CEN8 ≥ 2.0 or the average number of FGFR1 signals per cell >6 or >10% of tumor cells containing ≥15 FGFR1 signals. FGFR1 protein expression was determined by immunohistochemistry (IHC). Expression was defined as staining intensity 2+ or 3+ (graded from 0 to 3+) in >1% of the cancer cells.

Statistical calculation of correlation between FISH and IHC results (74 pts) was performed using the GraphPad Prism software using Spearman test.

Results

FGFR1 amplification was observed in 11/74 (14.86%) SQCLC tumors. The average FGFR1 gene copy number per cell ranged from 1.23 to 13.97 (mean: 3.61) while the mean FGFR1/CEN8 ratio was 1.27 (range: 0.53 - 4.35). The mean content of tumor cells with ≥15 FGFR1 copies was 10.19%. In IHC(+) tumors (22/74, 29.73%) the percentage of stained cancer cells with intensity ≥2 was low - only 12/74 (16.22 %) samples.

The FISH and IHC results were consistent in 79,73% SqCC tumors (n=59), 55/74 (74,32%) tumors were double-negative, while only 4/74 (5,41%) double-positive. 15/74 pts results were discordant: 7/74 (9,46%) IHC(-) FISH(+), while 8/74 (10,81%) pts IHC(+) FISH(-). There was no correlation between FGFR1 amplification and FGFR1 protein overexpression (P = 0.466; r = 0.086) in the analyzed series of 74 SqCLC tumors.
Conclusion

While we demonstrated relative SqCLC tumor homogeneity in terms of FGFR1 amplification and expression for as many as 74% of tumors, most were double negative. In samples demonstrating any positivity, FGFR1 amplification did not relate to protein expression. Therefore, further more detailed comparative evaluation of FGFR1 gene expression or FGFR1 locus might be informative to better understand the determinants of response to FGFR inhibitors

**Keywords:** FGFR1 expression, amplification, biomarker, squamous cell lung cancer