**PROGNOSTIC SIGNIFICANCE OF SHP2 EXPRESSION IN NON-SMALL LUNG CANCER PATIENTS**

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Background

Lung cancer remains the leading cause of cancer-related death across the world. Eighty-five percent of lung cancers are of the non–small cell type (NSCLC). Use of immune checkpoint inhibitors alone or in combination with chemotherapy, has become a gold standard for these patients. SHP2 is a nonreceptor, ubiquitous protein tyrosine phosphatase required for the growth of KRAS mutant and ALK-rearranged NSCLC. In T cells, SHP2 is an intracellular molecule activated downstream of the PD-1 signaling pathway that suppresses T-cell activation and thereby antitumor immunity.

Methods

We examined the association between SHP2 expression and PD-L1 expression along with driver gene mutations in 259 Greek NSCLC patients. We also examined the possible correlation between SHP2 expression and clinical response to immunotherapy. SHP2 expression was estimated by immunohistochemistry (D50F2 Rabbit mAb) with any H-score ≥ 150 considered as positive. PD-L1 immunoexpression was defined using 22C3 PharmDx DAKO (mAb). Driver gene mutations were detected by Next Generation Sequencing (NGS). Data analysis was performed using SPSS v29.0.

Results

SHP2 positive expression was detected in 61 cases (23.5%). KRAS mutated patients with positive SHP2 expression showed a statistically significant benefit both in overall survival (OS) (p 0.033) and progression free survival (PFS) (p 0.003) compared to KRAS mutated SHP2 non-expressors irrespective of treatment. SHP2 expression is a strong prognostic factor as it was also independently correlated with PFS benefit (p 0.0024). Upon stratification according to treatment, SHP2 positive patients who received immunotherapy as first line therapy showed a statistically significant benefit in PFS compared with non expressors receiving the same treatment (p 0.0076).

Conclusions

Positive SHP2 expression appears to offer PFS benefit regardless of treatment option while this benefit is expanded and enhanced in patient group receiving immunotherapy. Of great interest is the fact that KRAS mutated/SHP2 expressors showed OS and PFS benefit compared to KRAS mutated/SHP2 non-expressors. KRAS mutations’ poor prognostic effect is well documented. SHP2 expression may have a protective role in this patients’ group while may be an effective indicator of response to immunotherapy. Αdditional prospective studies are warranted to validate this finding.