Assessment of CTLA4 and TIGIT expression on CTCs and PBMCs of patients with small cell lung cancer (SCLC)

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Background & objectives

Cytotoxic T lymphocyte antigen 4 (CTLA4) and T cell immunoreceptor with Ig and ITIM domains (TIGIT) are frequently expressed on tumor-infiltrated immune cells (TILs) in SCLC tumors with potential prognostic and therapeutic implications. Tumor cells may also exploit the expression of these immune checkpoints to escape immune surveillance. We herein aimed to investigate the distribution and role of CTLA4 and TIGIT expression on tumor cells and immune cells in the peripheral blood (PB) of patients with SCLC.

Methods

PB was obtained from 72 SCLC patients prior to first-line treatment (limited disease: 16, extensive disease: 56). Peripheral blood mononuclear cell (PBMC) cytospins were stained for CK/CD45 and CK/CTLA4/TIGIT. Samples were analyzed *via* fluorescence microscopy.

Results

CTCs (CK+/CD45- cells) were identified in 29/72 (40.3%) patients (total CTCs: n=94, mean: n=3.2). CTLA4+ CTCs and TIGIT+ CTCs were identified in 44.8% and 24.1% of CTC-positive patients, respectively, and represented the 15.2% and 10.9% of total CTCs, respectively. The majority of patients harbored CTCs negative for both markers (58.6%), or CTCs expressing one marker only (37.9%), whereas 17.2% had CTCs positive for both CTLA4 and TIGIT (CTLA4+/TIGIT+). Regarding PBMCs, CTLA4 and TIGIT expression was demonstrated in 94.4% and 100% of patients, respectively, showing an increased distribution among CTC-positive as compared to CTC-negative patients (mean % CTLA4+ PBMCs: 33.8% versus 23.7%, p=0.030; mean % TIGIT+ PBMCs: 44.7% vs 28.4%, p=0.002, respectively). CTLA4+/TIGIT+ CTCs were exclusively identified in patients with extensive rather than limited disease (8.9% versus 0% of patients, respectively, Fisher's exact test, p=0.215). CTLA4+/TIGIT+ CTCs were more frequently detected among non-responders as compared to responders, both at the first evaluation (28.6% versus 1.9% of patients, respectively, p=0.035), as well as at the second evaluation of treatment (20% versus 2.3% of patients, respectively, p=0.030).

Conclusion

CTLA4+ PBMCs and TIGIT+ PBMCs are more frequently detected in CTC-positive patients, and CTLA4+/TIGIT+ CTCs are associated with disease progression. These results provide first evidence on the expression of CTLA4 and TIGIT on CTCs and PBMCs in SCLC and imply that their detection in PB is involved in metastasis and disease progression in SCLC.