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The relationship between nivolumab pharmacokinetics and cancer cachexia biomarkers in patients with metastatic non-small cell lung cancer (NSCLC)

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Background

In patients with NSCLC, a strong inverse relationship between nivolumab clearance and response has been observed, with cachexia as a proposed confounding factor. To further explore underlying mechanisms, we assessed the relationship between nivolumab pharmacokinetics (PK), body composition and serum cachexia biomarkers.

Methods

Patients with advanced NSCLC treated with nivolumab monotherapy according to standard of care were included. The model structure was obtained from a published PK-model. Clearance and covariate relationships (cachexia parameters and patients characteristics) were stepwise assessed in this cohort. At baseline, C-reactive protein (CRP), interleukin (IL)6, growth differentiation factor (GDF) 15 and -8, adiponectin and leptin were measured. Skeletal muscle mass (SMM), subcutaneous and visceral adipose tissue (SAT and VAT) were measured at the first lumbar vertebra on computed tomography images at baseline, week 6, and week 12 and adjusted for height squared (SMMi, VATi, SATi). Early body weight loss was defined as >2% weight loss during the first 42 (\pm 10) days.

Results

Out of 154 patients, 149 provided samples for nivolumab PK analysis, and 117 for serum cachexia biomarkers. Nivolumab clearance showed a significant positive association with GDF15 ($p < 0.001$) and CRP ($p < 0.001$). Men showed higher clearance compared to women ($p < 0.001$). Weight loss and changes in SMMi were not significantly associated with clearance. The median concentration of GDF15 was 2406 pg/ml (IQR 1655-3900). Similar GDF15 concentrations were found in patients with early weight loss. Patients with elevated GDF15 levels (>2000 pg/ml) had significantly worse overall survival (HR = 1.70, 95%CI 1.13-2.54).

Conclusions

Baseline GDF15 was significantly associated with nivolumab clearance and with poor survival in patients with advanced NSCLC. As GDF15 is known to inhibit immune infiltration in tumors and to induce cachexia, this might be the strongest confounder between nivolumab clearance and survival. Future research is required to explore how GDF15 production is stimulated and to unravel its exact biological mechanism of action.

Clinical trial identification

NL-OMON27631, Date of registration: 06-02-2018.

Legal entity responsible for the study

The authors.

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Disclosure

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