Background: Immune checkpoint inhibitors improve survival of patients with advanced melanoma. Combination anti-PD1 and anti-CTLA4 therapy improves the response rate compared to single agent anti-PD1, at the expense of far greater toxicity. While efforts have been made to identify biomarkers to predict treatment response, there are no biomarkers to predict for immunotherapy toxicity.

Methods: 188 plasma samples from 99 patients (discovery cohort – 50 patients, validation cohort – 49 patients) receiving combination anti-PD1 (nivolumab or pembrolizumab) and anti-CTLA4 (ipilimumab) were studied. The expression of 65 cytokines, measured at baseline (PRE) and early during treatment (EDT: week 1-3), was correlated with immune-related toxicity, defined as toxicity that warranted discontinuation of treatment and administration of high dose steroids (> 50 mg PO prednisolone equivalent), within 6 months of starting treatment (hypophysitis requiring steroid replacement was excluded).

Results: Toxicity rates were comparable between the discovery and validation cohorts, 21/50 (42%) and 22/49 (45%) respectively. The median expression of all cytokines was significantly higher in patients with immune-related toxicity, compared to patients without toxicity in both the discovery cohort (PRE; p = 0.01, EDT; p < 0.01) and validation cohort (PRE; p = 0.03, EDT; p = 0.02). In addition, the median expression of six pro-inflammatory cytokines associated with autoimmune disease (IFN-γ, IL-1β, IL-17A, IL-1α, IL-1β, IL-12) was significantly higher at baseline and EDT in patients with toxicity; discovery (PRE and EDT, p < 0.01) and validation (PRE, p < 0.01; EDT, p = 0.01). Expression of FGF-2, IL-12P70, IL-13, IL-1β, IL-2, MIG-JIF and VEGF-A was also significantly higher in patients with toxicity at PRE and EDT, in both the discovery and validation cohorts, compared to patients without toxicity.

Conclusions: Elevated levels of circulating cytokines at baseline and EDT predict development of immune-related toxicity. Pre-treatment measurement of circulating inflammatory cytokines may have an important role in treatment selection for metastatic melanoma patients.

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