Background Immune checkpoint inhibitors (ICIs) often lead to immune-related adverse events (irAEs) with effects ranging from treatment interruption to mortality. Most irAEs are treated with corticosteroids despite mounting evidence to suggest that corticosteroid treatment may blunt antitumor efficacy. There is a paucity of data on biomarkers that predict irAEs or characterize inflammatory changes during irAEs or steroid use. We sought to identify changes in cytokines that correlate with irAEs and may suggest inflammatory mechanisms that enable rational therapies. We also aimed to study the impact of steroid treatment on cytokine levels to better understand their immunomodulatory effect.

Methods We analyzed longitudinal levels of 34 cytokines in 52 melanoma patients receiving ICIs who developed irAEs. Luminex assay was performed on serum at baseline, 1, 2, and 3 months after starting ICI. Baseline cytokine levels were compared with incidence and grade of irAEs. Cytokine fold-change was compared between patients who did not develop irAEs, patients who developed irAEs without receiving steroids, and patients who developed irAEs who received steroids during the longitudinal profiling period.

Results 33/52 (63.5%) patients were male and median age was 70.5 years. 47 patients (90.4%) received anti-PD1 monotherapy, 4 patients (7.7%) received anti-CTLA-4 monotherapy and one patient received combination therapy (1.9%). Twenty-eight patients (53.8%) developed grade 1–2 irAEs and 24 patients (46.2%) developed grade 3–4 irAEs. There were no differences in cytokine levels between patients with grade 1–2 vs. grade 3–4 irAEs. Patients with dermatitis (N = 8) had significantly higher baseline Ang-1 (p = 0.006) and CD40L (p = 0.005, figure 1A). Patients with pneumonitis (N = 4) had
significantly higher baseline IL-17 (p = 0.009, figure 1B). There was a trend towards lower GCSF levels in patients developing colitis (N = 8, p = 0.08, figure 1C). We observed a harmonization of cytokine fold-change in patients who developed irAEs without receiving steroids: 269/276 (97.5%) of pairwise comparisons exhibited fold-change in the same upwards or downwards direction (figure 2). In contrast, corticosteroid treatment in patients with irAEs appeared to alter cytokine fold-change to a discordant pattern (214/276, 77.5%) mirroring patients who did not develop irAEs during the longitudinal profiling period (213/276, 77.2%). Example patient timelines are shown in figure 3.

Conclusions Baseline cytokine levels correlate with specific irAEs in melanoma patients receiving ICIs. IrAEs appear to drive a concordant pattern of cytokine fold-change, which is disrupted by corticosteroid administration. These findings should be validated in larger cohorts.

Ethics Approval Patients were identified from DFCI’s melanoma bio-specimen banking protocol (DFCI protocol 05-042)

REFERENCES

INCIDENCE OF THROMBOEMBOLISM (TE) IN PATIENTS WITH MELANOMA RECEIVING IMMUNE CHECKPOINT INHIBITOR (ICI) THERAPY AND ITS ADVERSE IMPACT ON SURVIVAL

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Background Little is known about rates of arterial thromboembolism (ATE) and venous thromboembolism (VTE) in patients with melanoma on ICI. We assessed incidence and outcomes of ATE and VTE in patients with melanoma receiving ICI.

Methods We conducted a retrospective cohort study of patients with melanoma receiving ICI from July 2015 through December 2017 at Cleveland Clinic. TE including VTE events of deep venous thrombosis (DVT), pulmonary embolism (PE), visceral vein thrombosis (VVT), and ATE events of myocardial infarction (MI), stroke, or transient ischemic attack (TIA) after ICI initiation were identified. Overall survival (OS) from ICI initiation was estimated by Kaplan-Meier and Cox hazard models; associations between TE, ICI regimen, and clinical risk factors were evaluated using log-rank test.

Results The study population comprised 228 patients with median age 65 (23–91) years, 67% male, and median follow up 27.3 months. Pembrolizumab was most commonly used (38.7%), followed by combination ipilimumab plus nivolumab (29.4%), ipilimumab (20%), and nivolumab (12.3%). Most had stage IV disease (81.1%) and 11% had brain metastases (BM) at treatment initiation. Fifty-one TE events occurred in 47 patients (20.6%), including 37 (16.2%) VTE and 14 (6.1%) ATE. Of VTE, DVT comprised 46.0%, PE 24.3%, DVT+PE 21.6%, VVT 5.4%, and DVT+VVT 2.7%. Of ATE, stroke comprised 57.2%, MI 35.7%, and TIA 7.1%. Of all TE events, 72% resulted in hospitalization and 19% resulted in clot-related mortality. Cumulative incidence of TE after ICI initiation was 9.3% (95%CI,6.0–13.6%) at 6 months, and 16.0% (95%CI,11.6–21.2%) at 12 months. The 6- and 12-month VTE cumulative incidence rates were 8.0% (95% CI,4.9–12.0%), and 12.9% (95%CI,8.9–17.7%), respectively. The 6- and 12-month ATE cumulative incidence rates were 2.2% (95%CI,0.84–4.8%), and 4.5% (95%CI,2.3–7.8%), respectively. The 6- and 12-month VTE cumulative incidence rates were higher with combination ICI than single agent (16.7% vs. 5.0% and 21.3% vs. 9.5%, respectively; p=0.02) (figure 1). Risk factors associated with VTE in univariate analysis included BM, stage IV disease, combination ICI, and Khorana score ≥1 (p<0.05 for all). In multivariate analysis, combination ICI (HR 2.21; [95%CI,1.04–4.72]; p=0.04) and Khorana score ≥1 (HR 2.48; [95%CI,1.18–5.20]; p=0.02) remained significantly associated with VTE. Of patients without BM, OS was worse in patients with TE compared to those without (3-year OS 34.9% vs. 62.9%; HR 1.84; [95% CI,1.16–2.93]; p<0.001), when adjusted for age, stage, and Khorana score (figure 2).