846 MYELOID REPROGRAMMING BY JAK INHIBITION ENHANCES CHECKPOINT BLOCKADE IMMUNOTHERAPY

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Background Activation of anticancer T cell immunity by checkpoint inhibition has become a key tool in the clinical management of cancer, but efficacy is limited in part by the suppressive activity of myeloid cells. Reprogramming myeloid cells from a suppressive into an immune-enhancing state is a goal of significant translational interest. Using preclinical and clinical studies, we investigated the potential of JAK inhibitors to enhance the efficacy of checkpoint inhibitors in a myeloid-dependent manner.

Methods The combination therapy of systemic treatment with the JAK inhibitor ruxolitinib with anti-PD1 + anti-CTLA4 was evaluated for efficacy and biomarkers compared to checkpoint inhibitors (ICI) alone in four murine immunocompetent models of cancer. Tumor-infiltrating, blood and lymphoid organ immune cells were phenotyped using single-cell transcriptomics, functional assays and flow cytometry. The combination therapy was clinically tested in an investigator-initiated Phase I/II clinical trial of ruxolitinib with nivolumab in relapsed or refractory Hodgkin lymphoma (NCT03681561). Patients who previously failed to respond to ICI received ruxolitinib for 1 week then nivolumab every 4 weeks concurrent with ruxolitinib. Hematologic, transcriptomic and flow cytometric analyses were performed on peripheral blood collected at baseline and after ruxolitinib treatment.

Results The ruxolitinib + ICI combination was superior to ICI in 3/4 of the tumor models examined in controlling tumor growth. Compared to ICI alone, tumor sizes were reduced by >50% in the MC38 (mean volume 123.1 vs 283.2 mm^3, n=9 per group, p=0.0094), LLC1 and A20 models (survival hazard ratio 0.47, n=30 per group, p=0.025). Remarkably, we observed a broad shift of tumor monocytes and granulocytes from a suppressive into an immunostimulatory state characterized by the expression of MHC-II and the ability to stimulate T cell proliferation. Depleting monocytic or granulocytic cells abrogated the beneficial effect of ruxolitinib. Hodgkin lymphoma patients in the ruxolitinib with nivolumab trial exhibited a disease control rate of 63% (12/19) including 5 complete responses. Ruxolitinib treatment in these patients did not impair T cell numbers or cytokine production but significantly reduced the neutrophil-to-lymphocyte ratio (NLR, mean difference -0.82, n=14, p=0.0023) and the percentage of $LOX1^+$ granulocytic suppressor cells in peripheral blood (mean 0.27 of baseline, p=0.0009). The reduction in NLR was significantly greater in complete responders than in progressive disease patients (mean -2.6 vs -0.58, respectively, p=0.023).

Conclusions The combination of ruxolitinib with ICI was effective in preclinical models and in a Phase I/II Hodgkin lymphoma clinical trial, identifying JAK inhibition with ICI as a promising myeloid-modulating immunotherapy.

Trial Registration The clinical trial identifier number is NCT03681561.

Ethics Approval This work was approved by the Institutional Review Boards of the University of Minnesota (STUDY00001341) and The Scripps Research Institute (IRB-19–7408, IRB-21–7803).