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Effects of Renin Angiotensin Pathway Inhibition on Efficacy of Anti-PD-1/PD-L1 Treatment in Metastatic Cancer

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Abstract : Inhibition of programmed death-1 (PD-1) or its ligand PD-L1 confers therapeutic efficacy in a wide range of solid tumor malignancies. Primary or acquired resistance can develop through activation of immunosuppressive immune cells such as tumor-associated macrophages. The renin angiotensin system (RAS) systemically regulates fluid and sodium hemodynamics, but components are expressed on and regulate the activity of immune cells, particularly of myeloid lineage. We hypothesized that inhibition of RAS would improve the efficacy of PD-1/PD-L-1 treatment. A retrospective analysis was performed through a chart review of patients with solid metastatic malignancies treated with a PD-1/PD-L1 inhibitor between 1/2013 and 6/2019 at Valley Hospital, a community hospital in New Jersey, USA. Efficacy was determined by medical oncologist documentation of clinical benefit in visit notes and by the duration of time on immunotherapy treatment. The primary endpoint was the determination of efficacy differences in patients treated with an inhibitor of RAS (ace inhibitor, ACEi, or angiotensin blocker, ARB) compared to patients not treated with these inhibitors. To control for broader antihypertensive effects, efficacy as a function of treatment with beta blockers was assessed. 173 patients treated with PD-1/PD-L-1 inhibitors were identified of whom 52 were also treated with an ACEi or ARB. Chi-square testing revealed a statistically significant relationship between being on an ACEi or ARB and efficacy to PD-1/PD-L-1 therapy (p=0.001). No statistically significant relationship was seen between patients taking or not taking beta blocker antihypertensives (p= 0.33). Kaplan-Meier analysis showed statistically significant improvement in the duration of therapy favoring patients concomitantly treated with ACEi or ARB compared to patients not exposed to antihypertensives and to those treated with beta blockers. Logistic regression analysis revealed that age, gender, and cancer type did not have significant effects on the odds of experiencing clinical benefit (p=0.74, p=0.75, and p=0.81, respectively). We conclude that retrospective analysis of the treatment of patients with solid metastatic tumors with anti-PD-1/PD-L1 in a community setting demonstrates greater clinical benefit in the context of concomitant ACEi or ARB inhibition, irrespective of gender or age. This data supports the development of prospective assessment through randomized clinical trials.

Keywords : angiotensin, cancer, immunotherapy, PD-1, efficacy
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