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Effect of Renin Angiotensin Pathway Inhibition on the Efficacy of Anti-programmed Cell Death (PD-1/L-1) Inhibitors in Advanced Non-small Cell Lung Cancer Patients- Comparison of Single Hospital Retrospective Assessment to the Published Literature

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Abstract : The use of immunotherapy that inhibits programmed death-1 (PD-1) or its ligand PD-L1 confers survival benefits in patients with non-small cell lung cancer (NSCLC). However, approximately 45% of patients experience primary treatment resistance, necessitating the development of strategies to improve efficacy. While the renin-angiotensin system (RAS) has systemic hemodynamic effects, tissue-specific regulation exists along with modulation of immune activity in part through regulation of myeloid cell activity, leading to the hypothesis that RAS inhibition may improve anti-PD-1/L-1 efficacy. A retrospective analysis was conducted that included 173 advanced solid tumor cancer patients treated at Valley Hospital, a community Hospital in New Jersey, USA, who were treated with a PD-1/L-1 inhibitor in a defined time period showing a statistically significant relationship between RAS pathway inhibition (RASi through concomitant treatment with an ACE inhibitor or angiotensin receptor blocker) and positive efficacy to the immunotherapy that was independent of age, gender and cancer type. Subset analysis revealed strong numerical benefit for efficacy in both patients with squamous and nonsquamous NSCLC as determined by documented clinician assessment of efficacy and by duration of therapy. A PUBMED literature search was now conducted to identify studies assessing the effect of RAS pathway inhibition on anti-PD-1/L1 efficacy in advanced solid tumor patients and compare these findings to those seen in the Valley Hospital retrospective study with a focus on NSCLC specifically. A total of 11 articles were identified assessing the effects of RAS pathway inhibition on the efficacy of checkpoint inhibitor immunotherapy in advanced cancer patients. Of the 11 studies, 10 assessed the effect on survival of RASi in the context of treatment with anti-PD-1/PD-L1, while one assessed the effect on CTLA-4 inhibition. Eight of the studies included patients with NSCLC, while the remaining 2 were specific to genitourinary malignancies. Of the 8 studies, two were specific to NSCLC patients, with the remaining 6 studies including a range of cancer types, of which NSCLC was one. Of these 6 studies, only 2 reported specific survival data for the NSCLC subpopulation. Patient characteristics, multivariate analysis data and efficacy data seen in the 2 NSLCLC specific studies and in the 2 basket studies, which provided data on the NSCLC subpopulation, were compared to that seen in the Valley Hospital retrospective study supporting a broader effect of RASi on anti-PD-1/L1 efficacy in advanced NSLCLC with the majority of studies showing statistically significant benefit or strong statistical trends but with one study demonstrating worsened outcomes. This comparison of studies extends published findings to the community hospital setting and supports prospective assessment through randomized clinical trials of efficacy in NSCLC patients with pharmacodynamic components to determine the effect on immune cell activity in tumors and on the composition of the tumor microenvironment.

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