immunotherapy of cancer

**ANTI-ANGIOGENIC THERAPY INDUCES T-LYMPHOCYTE INFILTRATION ASSOCIATED WITH POOR SURVIVAL IN METASTATIC RENAL CELL CARCINOMA PATIENTS**

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**Aim:** Renal cell carcinoma (RCC) is an immunogenic and proangiogenic cancer. Recently, anti-angiogenic therapy has been widely used for RCC management. The interaction between immune cell infiltration and anti-angiogenic treatment in RCC, and its association with patient survival, is unknown. We assessed the interaction between anti-angiogenic therapy and immune cell infiltration, and determined their impact on clinical outcome.

**Methods:** Tissue microarrays (TMA) with triplicate cores for each case were generated from formalin-fixed, paraffin embedded tissues from 33 unaffected kidneys, 41 untreated primary RCC, 42 bevacizumab and 39 sunitinib pretreated primary RCC from patients with metastatic RCC. Immunohistochemistry was used to evaluate the infiltration of immune cells. Staining quantitation was performed using a Vectra multispectral system (Perkin Elmer, Waltham, MA).

**Results:** Compared with normal kidney tissues, RCC tissues harbor more infiltrated immune cells, including CD3+ T cells, CD4+ T cells, CD8+ T cells, granzyme B+ T cells and CD68+ macrophages (p < 0.001). Both bevacizumab and sunitinib treatment increased CD4+ T cell infiltration from 7.63% to 15.26% and 16.33% (p < 0.01), and enhanced CD8+ T cell infiltration from 2.28% to 6.98% and 5.09% (p < 0.05), respectively. Importantly, the infiltration of CD4+ and CD8+ T cells was inversely correlated to overall survival (OS) and progression free survival (PFS) of bevacizumab and sunitinib pretreated RCC patients (p < 0.05). We further found that the anti-tumor activity of infiltrated T cells was probably suppressed by both increased infiltration of CD4+ FoxP3+ regulatory T cells and enhanced expression of checkpoint ligand PD-L1 on tumor cells. The infiltration of CD68+ macrophages also increased after sunitinib treatment (20.27% vs 25.16% percent, p < 0.05) but not after bevacizumab treatment (20.27% vs 21.29%, p > 0.05), and macrophage infiltration was not associated with patient survival (p > 0.05).

**Conclusions:** Our study shows that anti-angiogenic therapy increases T cell infiltration in primary RCC tumors of a subset of patients with metastatic disease, and this T cell infiltration is associated with worse clinical outcome. These findings will guide further studies on the mechanistic drivers of T cell infiltration and the impact of these cell populations on therapy response.

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