special symposium: beyond tumour heterogeneity: new pathways in kidney cancer

IMMUNOTHERAPY: MYTH OR REALITY?

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An improved understanding of kidney cancer (KC) tumor biology has led to major advancements in the treatment of patients with metastatic disease. While agents that target the VEGF and mTOR pathways prolong survival, resistance develops for most patients within the first year of therapy. Agents that lead to durable remissions are of urgent need to patients living with this disease. For two decades, the clinical experience with high-dose bolus IL-2 has served as proof of principle that immunotherapy can produce durable responses in a small percentage of KC patients. Basic and translational investigation to elucidate the molecular mechanisms that govern the interaction between a tumor and its host immune response has helped to explain why immunotherapies too often fail to achieve satisfactory results. In KC, obstacles to effective immunotherapy may include the physiological down-modulation of the immune response through the expression of programmed death ligand-1 (PD-L1) on tumor cells and cytotoxic T-lymphocyte antigen-4 (CTLA-4) on activated T cells, which serve to restrict the cytolytic function of tumor-infiltrating T lymphocytes, the proliferation of regulatory (CD4+ CD25+) T cells (T-regs) in response to nonspecific cytokine administration, and the immunosuppressive effects of elevated circulating VEGF levels and myeloid-derived suppressor cells (MDSC). These insights have encouraged investigators to pursue agents that block T-cell regulation (e.g., PD-1 and CTLA-4 antibodies), inhibit tumor-induced immunosuppression (e.g. PD-L1 antibody) and more specifically activate T-cells (e.g. CD-137 antibody, IL-21), and dendritic cells (e.g. AGS-003). Several of these approaches have shown encouraging efficacy in early trials both as single agents and in combination with standard therapies. However, for "targeted immunotherapy" to reach its full potential, significant work will need to be done to improve patient selection by refining proposed predictive biomarkers and overcome resistance mechanisms through the development of combination regimens.