

KIDNEY CANCER UPDATE

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The Effect of Interleukin 1 Beta Blockade on the Tumor Microenvironment

Based on a presentation by Charles G. Drake, MD, PhD, at the International Kidney Cancer Symposium 2020, November 6-7, Virtual

Preclinical data suggest that interleukin 1 beta (IL-1 β) blockade in combination with tyrosine kinase inhibition can alter the tumor microenvironment (TME) in kidney cancer, according to a presentation by Charles G. Drake, MD, PhD. The combination may even be synergistic, said Dr Drake, who previously directed genitourinary oncology at New York-Presbyterian/Columbia University Irving Medical Center; he now leads immuno-oncology at Janssen Research & Development. Columbia is currently conducting a clinical trial evaluating neoadjuvant IL-1 β blockade in combination with programmed death 1 (PD-1) inhibition.

Biology of the Tumor Microenvironment

Dr Drake began by giving an overview of the types of cells in the TME that suppress the antitumor response to renal cell carcinoma (RCC). These include CD4 $^{+}$ regulatory T cells (Tregs), which inhibit the ability of cytotoxic CD8 $^{+}$ T cells to kill tumors. Granulocytic myeloid-derived suppressor cells (MDSCs), which are related to neutrophils and are attracted into tumors through IL-8 and the CXCR2 pathway, are a second suppressive cell type. Monocytic MDSCs, which express CD14 and are likely attracted to the TME by the cytokine IL-1 β , are a third cell type. Tumor-associated macrophages that express M2, CD163, and other markers are a fourth cell type. A key biochemical mediator in this milieu is free adenosine, which binds to the adenosine A2A receptor on several of the cell types listed above. Agents blocking A2A signaling have shown activity in early RCC trials.

Research in Cardiovascular Disease

Dr Drake said his group became interested in IL-1 β on the basis of research in cardiovascular disease. As a result of data showing that the inflammation driving atherosclerosis and leading to myocardial infarction is at least in part mediated by innate cytokines such as IL-1 β , Ridker

and colleagues conducted a randomized, placebo-controlled trial of more than 10,000 patients who had previously experienced a myocardial infarction. They found that IL-1 β blockade with the agent canakinumab (Ilaris, Novartis) not only significantly reduced the risk for a second cardiovascular event but also significantly decreased the risk for a new cancer diagnosis. The hazard ratio for the development of any fatal cancer decreased from 0.86 to 0.78 to 0.49 as the canakinumab dose was increased from 50 to 150 to 300 mg, respectively. The effect was even more pronounced in lung cancer; the hazard ratio was 0.23 among patients who received the highest dose of canakinumab vs those who received a placebo. The findings were especially surprising in that the data had been collected because of concerns that IL-1 β blockade might lead to an increase in the incidence of cancer.

Preclinical Studies in Kidney Cancer

Following these intriguing results, “We sought to model this in kidney cancer,” said Dr Drake. He said that his team’s study was based on RenCa mouse renal adenocarcinoma cells, one of the best modeling options available when they began. The research, which was recently published online in *Clinical Cancer Research* with Aggen as the first author, showed that IL-1 β blockade slowed tumor growth, PD-1 inhibition slowed tumor growth a bit more, and a combination of IL-1 β blockade and PD-1 inhibition slowed tumor growth the most. Mechanistically, the Drake laboratory found that although IL-1 β blockade had little effect on the numbers of CD8 $^{+}$ T cells or CD4 $^{+}$ T cells, it decreased M2 macrophages, known as “bad macrophages,” and increased M1 macrophages, known as “good macrophages.” The use of IL-1 β blockade “significantly increased” the ratio of M1 to M2 macrophages, Dr Drake said.

The results were even more impressive when IL-1 β blockade was combined with the multitargeted tyrosine kinase inhibitor (TKI) cabozantinib (Cabometyx, Exelixis).

IL-1 β blockade and cabozantinib each decreased tumor weight independently, but “the combination had a more pronounced effect.”

Dr Drake said that his team had expected to see an increase in interferon gamma with IL-1 β inhibition, on the basis of increased secretion of antitumor T-cell cytokines, but that did not occur. They did see a decrease in IL-1 β , as expected, and a small decrease in IL-6. He said they were especially pleased to see a decrease in keratinocyte chemoattractant (KC)/human growth-regulated oncogene (GRO), which is one of several murine analogs of IL-8, because recently published research by Schalper and colleagues has shown that IL-8 is a predictive marker for response to PD-1 therapy. “It could be that you can fix multiple problems in the tumor microenvironment by blocking IL-1 β in combination with cabozantinib,” he said, inasmuch as IL-1 β is an upstream pathway.

Complexity of the Immune Tumor Microenvironment

The researchers used 28-color flow cytometry to stain the tumor microenvironment and characterize both the myeloid and T-cell populations. These studies revealed a fairly large number of distinct myeloid subsets, especially within the F4/80 population and the Ly6G population. This previously unappreciated complexity was also noted in the T-cell population, which showed an impressive number of clusters of both CD4+ cells and CD8+ cells. “The bottom line of this work is that there are multiple, very clear subpopulations of both T cells and myeloid cells in the tumor microenvironment,” said Dr Drake. In murine models, several of these variations were associated with treatment.

Ongoing laboratory studies led by Aleks Obradovic, an MD/PhD candidate in systems biology, are analyzing the TME in patients with clear cell RCC who are undergoing surgical resection; the group has looked at samples from 11 patients so far. The research is focused on both the tumor cells and the adjacent normal cells and is differentiating between CD45+ and CD45- cells, generating 4 populations for each patient to be analyzed with single-cell RNA sequencing. Early results from this work show that human samples display a cell cluster diversity similar to the diversity seen in mouse samples, with multiple populations of natural killer cells, B cells, and T cells. Only a fraction of these cells, however, are overrepresented in tumors vs adjacent tissue, and only a subfraction of those are associated with tumor stage. “We did find one population of macrophages that is associated with stage,” said Dr Drake. Furthermore, that macrophage

signature “beautifully correlates with recurrence,” he said. He added that his group is collaborating with Dr Brian Rini and colleagues at Vanderbilt University to validate the prognostic signature discovered at Columbia.

A Neoadjuvant Trial of IL-1 β Blockade in Renal Cell Carcinoma

To apply their studies clinically, the Columbia team is conducting a phase 1 clinical trial called SPARC-1, led by Dr Matthew C. Dallos, to examine the use of PD-1 inhibition with spartalizumab plus IL-1 β blockade with canakinumab in patients who have aggressive, nonmetastatic clear cell RCC (NCT04028245). So far, 3 of 14 patients have received 2 doses of the combination therapy 4 weeks apart, followed by radical nephrectomy 2 weeks after the second dose. The trial was designed by Dr Aggen, who is now at Memorial Sloan Kettering Cancer Center; Novartis is supporting the research.

Dr Drake said that although the overall data are not yet ready to share, flow cytometry and single-cell RNA sequencing in the first couple of patients have confirmed an increase in the M1-to-M2 ratio following treatment. This result is nearly identical to that seen in the group’s murine studies.

Conclusion

Dr Drake concluded his presentation by saying that IL-1 β blockade re-programs the myeloid component of the TME in a mouse model of kidney cancer. “We’ll see if it does the same thing in patients,” he said. He added that if the positive results with IL-1 β blockade and PD-1 inhibition are unsurprising, still more intriguing is the combination IL-1 β blockade with the TKI cabozantinib. “Perhaps the field needs to move away from blindly combining all of our agents with PD-1 blockade,” Dr Drake concluded, citing the cabozantinib/IL-1 β blockade concept as a data-driven alternative.

Suggested Readings

Aggen DH, Ager CR, Obradovic AZ, et al. Blocking interleukin-1 beta promotes tumor regression and remodeling of the myeloid compartment in a renal cell carcinoma model: multi-dimensional analyses [published online November 4, 2020]. *Clin Cancer Res*. doi:10.1158/1078-0432.CCR-20-1610.

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Schalper KA, Carleton M, Zhou M, et al. Elevated serum interleukin-8 is associated with enhanced intratumor neutrophils and reduced clinical benefit of immune-checkpoint inhibitors. *Nat Med*. 2020;26(5):688-692.