GENITOURINARY CANCER IN FOCUS

Current Developments in the Management of Genitourinary Cancer

Section Editor: Andrew J. Armstrong, MD

The Microbiome in Kidney Cancer

Shahla Bari, MD
Assistant Professor, Genitourinary Oncology
Seidman Cancer Center
Case Western Reserve University
Cleveland, Ohio

H&O Does the microbiome in the skin or gut of patients with kidney cancer differ from that of persons without the disease?

SB We do not know how the skin microbiomes of patients who do and do not have kidney cancer may differ; most of the work regarding the skin microbiome has been in the context of skin cancers such as squamous cell skin cancer and melanoma. We also do not have robust data identifying differences in the gut microbiomes of patients with and without kidney cancer,[1,2] although we do see differences between patients who do and do not respond to treatment.

The gut microbiome is important in many cancers because it modulates our immune responses, with an immunosuppressive environment predisposing people to certain cancers. Two examples of beneficial bacteria are *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*, both of which are associated with better responses to immunotherapy in melanoma, lung cancer, and kidney cancer. Another relevant bacterium is *Enterocloster clostridioformis*, except that elevated levels are found in cancer patients who do not respond to immunotherapy.[3]

H&O What do we know about the microbiome of the urinary tract and kidneys in those with and without kidney cancer?

SB The data regarding the urinary microbiome are inconsistent, in large part because some studies examine urine that has been caught midstream whereas others report microbial taxa in specimens collected via catheterization. We have seen that people with kidney cancer are more likely to have elevated levels of *Staphylococcus epidermidis* in their urinary microbiome.[4] This common skin bacterium is associated with infections in immunocompromised patients. Some investigators have also reported a preponderance of *Gardnerella* and *Enterococcus* in the urine of patients with clear cell renal cell carcinoma (RCC),[5] but the data are inconsistent, and more studies using similar methods of collection, processing, and analysis are needed to better characterize the urinary microbiome of patients with RCC.

The more important connection relates to the kidney microbiome. Multiple studies have found differences between the bacterial loads of *Trachelomonas,*[6] *Micrococcus*, *Streptococcus*, and *Fusobacterium nucleatum* in tumor tissue and in matched normal tissue.[7] Additional studies have noted differences in the microbiome composition of the kidneys of patients who have kidney cancer and those who have renal cysts. However, the bacteria associated with response continue to be divergent across studies and not likely to be reproducible because of differences in methods of sample collection, processing, and analysis. Most of the research on the intratumoral microbiome is based on samples collected after pathology review, which could be biased owing to contamination from the environmental microbiome. Of late, I have seen studies reporting tumor microbial composition in fresh tumor and adjacent normal tissue.[7,8] I think we should focus on conducting rigorous studies that examine tumor and matched normal samples collected in an operating room with appropriate sterility controls.

Another factor that may be associated with divergent results of microbiome composition among studies is the depth of genomic analysis in terms of the bacteriome.

When we analyze various types of bacteria in the microbiome, we need to go beyond the genus and species to evaluate at the strain and substrain resolution. For example, *Escherichia coli* as a species is generally considered a commensal bacterium that provides benefits to the human ecosystem, but *E. coli* at O157:H7 can cause hemolytic uremic syndrome, kidney failure, and even death. Because phenotypes can differ widely between substrains of the same species, it is critical that microbiome analysis move to deeper sequencing and, more importantly, functional sequencing.

H&O How might the gut microbiome affect toxicity due to immunotherapy?

SB Although we have few data looking at immune-mediated adverse events and the microbiome, we know that a subset of patients who are deep and durable responders are also those who experience greater toxicity, a phenomenon called the efficacy-toxicity coupling effect. For example, high levels of the *Faecalibacterium* species and the Firmicutes[9] phylum have been associated with a higher incidence of immune-mediated colitis and other toxicities. Similarly, some data sets have found an association of high levels of *Lachnospiraceae* and *Streptococcus* with grade 3/4 immune-mediated adverse events.[10]

H&O Are there any evidence-based clinical recommendations physicians can provide to patients to enhance their microbiome-mediated responses to immunotherapy?

SB No consensus-based document has been published at this point, although various groups, including ours, are working to develop consensus guidelines as part of the ECOG-ACRIN Cancer Research Group. On the basis of the data we have so far, we can recommend a high-fiber diet. A clinical survey study from MD Anderson Cancer Center found that patients receiving immunotherapy for melanoma had longer progression-free survival if they ingested at least 20 g of fiber per day. Further, every increase of 5 g in daily dietary fiber intake corresponded with a 30% lower risk of progression or death after adjustment for clinical factors.[11] Preclinical studies have found an association between better responses to immunotherapy and the use of prebiotics, which provide nutrition to the microbiome.[12,13]

A study that our institution is about to publish looked at the use of time-restricted eating, which consisted of fasting at night for 14 hours on 5 days of each week. This was a small study of 39 patients with metastatic head and neck cancer who were receiving single-agent pembrolizumab (Keytruda, Merck). We found that median progression-free survival (PFS) was 23 months for the patients in the fasting group vs 9 months in the control group, after controlling for clinical covariates. These are exciting times, with new interventions to improve treatment responses.

Probiotics, on the contrary, have shown divergent effects on immunotherapy response and toxicity. In the study of Spencer and colleagues, commercially available probiotic supplements were associated with worse responses to immunotherapy for melanoma,[11] although some studies have shown a beneficial effect of other probiotic formulations and rationally designed bacterial consortia in preclinical models and patient cohorts.[14,15] We have not pinpointed the reason, but one hypothesis is the loss of microbiome diversity associated with taking in a very high count of specific bacteria (eg, 2 billion *Bifidobacterium* or *Lactobacillus* organisms). The use of antibiotics, especially around the time of immunotherapy initiation, has also been associated with worse responses.[16]

So in summary, I would recommend that people consume more fiber, avoid commercial supplemental probiotics, and skip snacking after dinner. The prophylactic use of antibiotics should be restricted, and infections should be treated with the narrowest-spectrum antibiotics that provide appropriate coverage as opposed to a broad-spectrum approach. Emerging data support the idea that these steps can improve responses to immunotherapy, targeted therapy, and even chemotherapy.

H&O What are the most important studies of microbiome interventions that have been conducted in patients with kidney cancer?

SB Two important phase 1 studies looked at *Clostridium butyricum* strain 588 (CBM588), which is a butyrate-producing microorganism sold over the counter in Japan as a probiotic. The first study enrolled 30 patients who had metastatic clear cell kidney cancer. In this open-label study, patients were randomized in a 2:1 ratio to receive CBM588 or no CBM588; all patients received dual immune checkpoint inhibition with ipilimumab (Yervoy, Bristol Myers Squibb) and nivolumab (Opdivo, Bristol Myers Squibb). The researchers found that PFS was significantly longer in the patients who received CBM588 than in those who did not (12.7 vs 2.5 months).[17] The second study was similar in design except that it looked at immunotherapy plus targeted therapy, in this case nivolumab plus cabozantinib (Cabometyx, Exelixis), which reflects how we treat many of our patients with kidney cancer.[2] This study found that the overall response rate (ORR) was significantly higher in the CBM588 arm than in the control arm (74% vs 20%).[18]

Two trials have looked at the use of fecal microbiota transplant (FMT) in treatment-naive patients with metastatic RCC: TACITO[19] and PERFORM.[20] The randomized phase 2 TACITO trial evaluated whether FMT from people with a complete response to immunotherapy improved clinical outcomes in patients who were receiving pembrolizumab plus axitinib (Inlyta, Pfizer). The researchers found that median PFS was significantly longer with the addition of FMT than without (24 vs 9 months).

Obtaining fecal microbiota from people with a complete response to immunotherapy is difficult, so the phase 1 PERFORM trial took the approach of obtaining microbiota from healthy volunteers who did not have cancer and transplanting it into 20 patients who were about to begin combination immunotherapy. The researchers were able to show an ORR of 50%. Interestingly, very few patients had grade 3 or higher immune-related adverse events.[20]

A third aspect that the field is beginning to consider is the intratumoral microbial load itself—how much microbiota is present?

H&O What is the potential role of MAdCAM-1 as a prognostic biomarker for immunotherapy and a diagnostic test for microbiome imbalance?

SB The MAdCAM-1 protein helps direct leukocytes into mucosal and inflamed tissues. A recent study evaluated soluble MAdCAM-1 as a prognostic biomarker in 1051 patients who were receiving checkpoint inhibitors, tyrosine kinase inhibitors, or both for metastatic RCC.[21] The patients came from 3 studies: JAVELIN Renal 101, SURF, and NIVOREN. The researchers found that higher levels of soluble MAdCAM-1 at baseline were associated with better PFS and overall survival (OS), whereas lower levels were associated with an immunosuppressive gut microbiota profile dominated by *Enterocloster* species. Another interesting finding is that patients without an increase in their plasma MAdCAM-1 level during treatment were less likely to respond to treatment and had reduced PFS. These findings suggest that MAdCAM-1 might someday be used to identify which patients are in a dysbiotic state and prompt the use of microbial interventions.

H&O Could you talk about the phase 3 BIOFRONT study that your institution is launching?

SB We are very excited about the phase 3 BIOFRONT study, which builds directly on the phase 1 CBM588 research we discussed earlier. In BIOFRONT, approximately 700 patients with advanced RCC who are receiving standard-of-care treatment will be randomly assigned to receive either CBM588 or placebo (NCT07383441). The primary endpoint is PFS, and patients will be monitored for 5 years. It will be easy to accrue patients for this study because we already know that CBM588 has a good safety profile and signals of efficacy. If BIOFRONT shows that CBM588 can improve PFS and OS, the result will lead to a landmark improvement in how we treat patients with advanced kidney cancer.

H&O What other ongoing studies would you like to highlight?

SB City of Hope is conducting a study of CBM588 in patients with localized RCC who are scheduled to take 1 year of adjuvant pembrolizumab following nephrectomy (NCT07037004). The goal is to see whether this agent can help to prevent recurrence in the early-stage setting.

Cohort 1 of the phase 1 EV-2101 study followed up on 9 patients with intermediate- or poor-risk RCC who were negative for *Akkermansia* in their gut *and* found that the use of the *Akkermansia* supplement Oncobax-AK led to an ORR with immunotherapy of 50%.[22] An expansion phase of this study is examining Oncobax-AK at 6 times the original dose in patients with RCC or small cell lung cancer (NCT05865730).

H&O Is there anything you would like to add?

SB Although the field is very exciting, microbiome studies are marred by a lack of reproducibility and consistency, which may be attributed to several factors. We have historically relied on 16S sequencing, which enables us to evaluate taxonomy at the genus and species level of the microbiota. The same genus and species have vastly different functions and phenotypic expressions at the substrain level, so considering all *Akkermansia muciniphila* to be beneficial may not be the right strategy. Even though the cost of deeper sequencing is higher, research should be moving in the direction of deep sequencing to detect taxonomy at the substrain level and even deeper resolution, which may ultimately pave the path to reproducible and consistent biomarker development. Our laboratory

recently acquired a microbiome sequencer to enable deep sequencing in all our samples.

Another factor to consider is the phenomenon of functional redundancy. Two individuals with very different microbiota may respond in the same way to immunotherapy because different microbial communities can perform the same functions, a phenomenon called functional redundancy. It might be helpful to begin looking at microbial function in terms of microbial metabolites instead of the specific microbial taxonomy. Different taxa might produce the same metabolite performing the same immune function, resulting in similar phenotypes. As a result, microbial metabolism may play a complementary role in our pursuit of identifying biomarkers and druggable targets to improve treatment efficacy.

A third aspect that the field is beginning to consider is the intratumoral microbial load itself—how much microbiota is present? Dr Silver and her team found that the total quantity of intratumoral bacteria predicted response to checkpoint inhibitors, with a greater abundance associated with an immunosuppressive tumor microenvironment.[23]

To conclude, we have made significant strides in the context of the microbiome to predict and improve responses to immunotherapy. Still, many questions remain to be answered, and there is an urgent need for the field to be standardized to improve its reproducibility and scale its research.

Disclosures

Dr Bari has served as a speaker for Merck and OncLive and has served on the advisory board of Eisai.

References

1. Chen Y, Ma J, Dong Y, et al. Characteristics of gut microbiota in patients with clear cell renal cell carcinoma. *Front Microbiol*. 2022;13:913718.
2. Yin Z, Liu B, Feng S, et al. A large genetic causal analysis of the gut microbiota and urological cancers: a bidirectional Mendelian randomization study. *Nutrients*. 2023;15(18):4086.
3. Fidelle M, Rauber C, Alves Costa Silva C, et al. A microbiota-modulated checkpoint directs immunosuppressive intestinal T cells into cancers. *Science*. 2023;380(6649):eabo2296.
4. Kovaleva O, Podlesnaya P, Gratchev A. Resident microbiome of kidney tumors. *Oncol Rev*. 2024;18:1393664.
5. Heidler S, Lusuardi L, Madersbacher S, Freibauer C. The microbiome in benign renal tissue and in renal cell carcinoma. *Urol Int*. 2020;104(3-4):247-252.
6. Luis A Meza et al. Association between intra-tumoral microbiome and clinical benefit (CB) from immunotherapy (IO) in patients with metastatic renal cell carcinoma (mRCC) [ASCO abstract 4561]. *J Clin Oncol*. 2023;41(16)(suppl).
7. Wang J, Li X, Wu X, et al. Uncovering the microbiota in renal cell carcinoma tissue using 16S rRNA gene sequencing. *J Cancer Res Clin Oncol*. 2021;147(2):481-491.
8. Liss MA, Chen Y, Rodriguez R, et al. Microbiome within primary tumor tissue from renal cell carcinoma may be associated with PD-L1 expression of the venous tumor thrombus. *Adv Urol*. 2020;2020:9068068.
9. Chaput N, Lepage P, Coutzac C, et al. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. *Ann Oncol*. 2017;28(6):1368-1379.
10. McCulloch JA, Davar D, Rodrigues RR, et al. Intestinal microbiota signatures of clinical response and immune-related adverse events in melanoma patients treated with anti-PD-1. Nat Med. 2022;28(3):545-556.
11. Spencer CN, McQuade JL, Gopalakrishnan V, et al. Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response. Science. 2021;374(6575):1632-1640.
12. Zitvogel L, Kroemer G. Boosting the immunotherapy response by nutritional interventions. J Clin Invest. 2022;132(11):e161483.
13. Boucher E, Plazy C, Richard ML, et al. Inulin prebiotic reinforces host cancer immunosurveillance via gamma delta T cell activation. *Front Immunol*. 2023;14:1104224.
14. Tanoue T, Morita S, Plichta DR, et al. A defined commensal consortium elicits CD8 T cells and anti-cancer immunity. *Nature*. 2019;565(7741):600-605.
15. Sivan A, Corrales L, Hubert N, et al. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science*. 2015;350(6264):1084-1089.
16. Khan U, Ho K, Hwang EK, et al. Impact of use of antibiotics on response to immune checkpoint inhibitors and tumor microenvironment. *Am J Clin Oncol*. 2021;44(6):247-253.
17. Dizman N, Meza L, Bergerot P, et al. Nivolumab plus ipilimumab with or without live bacterial supplementation in metastatic renal cell carcinoma: a randomized phase 1 trial. *Nat Med*. 2022;28(4):704-712.
18. Ebrahimi H, Dizman N, Meza L, et al. Cabozantinib and nivolumab with or without live bacterial supplementation in metastatic renal cell carcinoma: a randomized phase 1 trial. *Nat Med*. 2024;30(9):2576-2585.
19. Porcari S, Ciccarese C, Heidrich V, et al. Fecal microbiota transplantation plus pembrolizumab and axitinib in metastatic renal cell carcinoma: the randomized phase 2 TACITO trial. *Nat Med*. 2026;32(4):1316-1324.
20. Fernandes R, Jabbarizadeh B, Rajeh A, et al. Fecal microbiota transplantation plus immunotherapy in metastatic renal cell carcinoma: the phase 1 PERFORM trial. *Nat Med*. 2026;32(4):1325-1336.
21. Alves Costa Silva C, Machaalani M, Saliby RM, et al. Soluble MAdCAM-1 as a biomarker in metastatic renal cell carcinoma. *Nat Med*. 2026;32(2):671-681.
22. Lisa Derosa et al. Phase 1 results of Oncobax-AK in combination with ipilimumab/nivolumab in advanced clear cell renal cell carcinoma (ccRCC; NCT05865730) [ASCO abstract 4529]. *J Clin Oncol*. 2025;43(16)(suppl).
23. Silver NL, Dai J, Kerr TD, Altemus J, Garg R, Simmons H, Alban T, Noel-Romas L, Makarov V, Shih DJH, Kumar SV, Santos A, Akbani R, Burgener A, Dwidar M, Gross N, Sikora AG, Sayour EJ, Stacy A, Jobin C, Chan TA, Ferrarotto R, McGrail DJ. Intratumoral bacteria are immunosuppressive and promote immunotherapy resistance in head and neck squamous cell carcinoma. *Nat Cancer*. 2026;7(1):80-97.