Biomarkers in metastatic renal cell carcinoma in the era of immune checkpoint inhibitors

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Provenance: This is an invited article commissioned by our Section Editor Dr. Xiao Li (Department of Urology, Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research, Nanjing Medical University Affiliated Cancer Hospital, Nanjing, China).

Comment on: Kamal Y, Cheng C, Frost HR, *et al.* Predictors of disease aggressiveness influence outcome from immunotherapy treatment in renal clear cell carcinoma. Oncoimmunology 2018;8:e1500106.

Submitted Jun 26, 2019. Accepted for publication Jun 30, 2019.
doi: 10.21037/atm.2019.07.13
View this article at: http://dx.doi.org/10.21037/atm.2019.07.13

Currently therapeutic landscape of renal cell carcinoma (RCC)

Metastatic renal cell carcinoma (mRCC) accounts for around 74,000 new cases and 15,000 deaths annually in the United States alone (1). Until recently, sequential use of agents targeting the vascular endothelial growth factor (VEGF) or mechanistic target of rapamycin (mTOR) pathways were the cornerstone of therapy for the vast majority of patients (2). The development of immune checkpoint inhibitors such as those targeting the programmed cell death-1 (PD-1) and the cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) pathways have led to a paradigm shift in the treatment of patients with metastatic RCC. The anti-PD-1 antibody nivolumab was the first immune checkpoint inhibitor to improve overall survival (OS) in mRCC patients who had progressed on prior VEGF targeted therapy (3). Subsequently, dual immune checkpoint inhibition with nivolumab in combination with the anti-CTLA-4 antibody ipilimumab showed significantly higher response rate, progression-free survival (PFS) and OS in treatment naïve patients with intermediate or poor risk RCC (4). Similarly, combination of the selective VEGF receptor tyrosine kinase inhibitor axitinib with either anti-PD-1 antibody pembrolizumab or the anti-PD-L1 antibody avelumab has demonstrated significantly improved outcomes compared to sunitinib across all RCC prognostic groups (5,6). These pivotal trials have established immunotherapy with either dual immune checkpoint inhibition or checkpoint inhibitors in combination with VEGF targeted agent axitinib as the new standard of care for previously untreated patients with RCC.

Immunotherapy biomarkers under investigation in RCC

Although immune checkpoint inhibitors have become an integral part of the treatment armamentarium of metastatic RCC and will be utilized for most patients either as first or subsequent line of therapy, there is significant heterogeneity in outcomes. While a small subset of patients experience durable long-term responses including complete responses, majority of patients experience disease progression with the median PFS being 11–14 months (4-6). Predictive biomarkers are critical for identifying patients less likely to respond to allow for potential therapy intensification or in case of patients likely to have durable responses, therapy discontinuation. Although the International Metastatic RCC Database Consortium (IMDC) risk model has proven to be prognostic in patients treated with VEGF targeted agents and immune checkpoint inhibitors, there continues to be a significant unmet need for genomic or molecular biomarkers reflecting tumor biology to guide optimal therapy selection and sequencing.

Tumor PD-L1 expression has been shown to have prognostic significance in several solid tumors such as non-small cell lung cancer and urothelial carcinoma and was one of the first biomarkers to be investigated in metastatic RCC. In the CheckMate 025 trial investigating nivolumab versus everolimus in patients who had progressed on prior VEGF targeted therapy, PD-L1 expression on tumor cells was assessed using the 28-8 Dako assay (3). The median OS was numerically higher in patients without PD-L1 expression (<1%; median OS: 27.4 months) compared to patients with ≥1% PD-L1 expression (21.8 months). The survival benefit of nivolumab was noted in all patients irrespective of PD-L1 status. Similarly, among the intermediate and poor risk patients included in the CheckMate 214 trial, nivolumab in combination with ipilimumab induced objective responses in 37% of patients without PD-L1 expression and 58% in PD-L1 positive patients (4). However, both PD-L1 positive and negative patients had improved OS with ipilimumab and nivolumab compared to sunitinib. Similarly, among the patients treated with axitinib in combination with avelumab in the JAVELIN Renal 101 study, patients with and without PD-L1 expression (assessed by Ventana SP263 immunohistochemistry) has similar PFS (PD-L1$^+$: 13.3 months *vs.* PD-L1$^-$: 12.5 months; HR: 0.89; 95% CI: 0.65–1.22; P=0.47) (7). These results highlight the challenges and limitations associated with using PD-L1 expression as a biomarker in RCC.

Expression of neoantigens on tumor cells and their recognition by the host immune system is critical for an effective anti-tumor immune response. High prevalence of non-synonymous mutations can result in increased tumor antigenicity and response to immune checkpoint inhibitors. This is supported by the established efficacy of immunotherapy seen in tumors with high mutational burden such as melanoma, lung cancer and urothelial carcinoma (8). Although RCC has a relatively lower overall mutational burden compared to these tumors, it has demonstrated comparable response rate with immune checkpoint inhibitors indicating that mutational burden alone may not be predictive of response to immunotherapy. Supporting this hypothesis, de Velasco *et al.* reported low prevalence of non-synonymous mutations in RCC. In their small cohort of 9 patients with metastatic disease treated with immunotherapy, mutational burden was not significantly different between non-responders and patients with an objective response (9). Similarly, Miao *et al.* also demonstrated that mutational burden was not predictive of response in RCC patients treated with checkpoint inhibitors (10).

Recent studies have also utilized whole transcriptome sequencing using RNA-seq to investigate gene expression signatures predictive of outcomes with immunotherapy. The phase 2 IMmotion150 trial evaluated the clinical efficacy of anti-PD-L1 antibody atezolizumab in combination with bevacizumab compared to sunitinib in patients with previously untreated metastatic RCC (11). Gene expression signatures reflecting angiogenesis (Angio^{high} *vs.* Angio^{low}) and effector T cell response (T_{eff}^{high} *vs.* T_{eff}^{low}) were evaluated as predictors of clinical outcomes across treatment arms. Among patients treated with sunitinib, Angio^{high} signature was associated with improved response rate and PFS compared to patients with Angio^{low} signature. However, there was no significant difference in PFS between the treatment arms in the Angio^{high} and T_{eff}^{low} groups. In contrast, patients with T_{eff}^{high} signature had significantly better PFS with atezolizumab and bevacizumab compared to sunitinib (HR 0.55; 95% CI: 0.32–0.95). The subsequent larger phase 3 IMmotion151 trial confirmed these biological groups and validated these gene expression signatures as potential biomarkers (12). In this study, the T_{eff}^{high} and Angio^{low} subsets had significantly improved PFS with the combination of atezolizumab and bevacizumab compared to sunitinib whereas no significant difference in outcomes between the treatment arms was observed in the Angio^{high} and T_{eff}^{low} subsets. Interestingly, patients in the Angio^{high} subset were more likely to have favorable risk disease (74% Angio^{high} *vs.* 26% Angio^{low}) per the Memorial Sloan Kettering Cancer Center (MSKCC) risk model while patients with sarcomatoid histology were more likely to have a T_{eff}^{high} signature compared to those without a sarcomatoid component (54% *vs.* 40%). In the JAVELIN Renal 101 study, a 26-gene expression signature consisting of genes involved in T cell receptor signaling, activation and proliferation, NK cell mediated cytotoxicity, chemokine secretion and other genes involved in anti-tumor immune response was associated with significantly improved PFS in patients treated with axitinib and avelumab combination (7). These findings highlight the inherent biological differences between these prognostic subgroups of RCC and the significant role biomarkers can play in optimal therapy selection.

Senescence as a biomarker of response to immunotherapy in RCC

Several prior studies have highlighted the potential role

of cellular senescence in both cancer prevention and carcinogenesis (13). Although senescent tumor cells do not proliferate, they demonstrate high metabolic and transcriptional activity and result in a senescence associated secretory phenotype (SASP) (14). Under physiologic conditions, SASP is regulated by p53 and in tumors with inactivating p53 mutations such as RCC, prolonged uncontrolled SASP response can contribute to tumor growth through increase in angiogenesis, increased tumor cell invasiveness and secretion of IL-6 and IL-8 (15-17). Conversely, SASP can also promote an inflammatory response through recruitment of immune cells to the tumor microenvironment resulting in tumor cell elimination (18).

In their recently published study in *Oncoimmunology*, Kamal *et al.* report that senescence could be a potential biomarker of aggressive disease and response to immunotherapy in metastatic RCC (19). They first utilized the gene expression and whole exome sequencing data from The Cancer Genome Atlas (TCGA) kidney cancer data set (KIRC) to investigate genomic factors associated with aggressive disease. Utilizing a previously published gene expression and whole exome sequencing data set consisting of patients with metastatic RCC treated with immunotherapy (10), they further investigated these genomic factors as potential biomarkers of response to immune checkpoint inhibitors. In their analysis based on the TCGA data set, they observed that metastatic RCC patients demonstrated significantly higher infiltrating immune cells in their tumors compared to patients without metastatic disease which correlated with expression of immune checkpoints and markers of immune activation. Increase in $CD8^+$ and $CD4^+$ T-cells was associated with worse outcomes while infiltrating dendritic cells predicted improved survival. Metastatic RCC group was also enriched in markers of TP53 inactivation mediated tumor senescence which correlated with immune activation and poor outcomes. Among the patients included in the immunotherapy dataset, high tumor senescence or expression of immunomodulatory molecules (e.g., PDCD-1, cGAS, GZMA, PRF1 and GZMB) by itself was associated with poor response to immunotherapy. However, patients with higher senescence and high expression of immunomodulatory molecules had improved outcomes with checkpoint inhibitors. Based on these findings, the authors propose that tumor senescence by itself could be a potential marker of adverse prognosis in patients with RCC. However, coupled with markers of immune activation, it could predict improved outcomes in patients with RCC treated with immunotherapy.

Conclusions

The development of immunotherapy represents a major advance in the treatment of mRCC. Several potential biomarkers of response have shown promise and are currently under investigation. The authors should be commended on their small but hypothesis raising study. Senescence could be a marker of aggressive disease in RCC and given its role in promoting inflammation in the tumor microenvironment, could predict response to immunotherapy in RCC. The findings warrant validation in larger datasets.

Acknowledgments

None.

Footnote

Conflicts of Interest: A Tripathi: Advisory Fee: Foundation Medicine; Research Funding to Institution: EMD Serono, Aravive Inc, Bayer, Clovis Oncology, Corvus Pharmaceuticals, WindMIL therapeutics. N Agarwal: Consultancy to Astellas, Astra Zeneca, Argos, BMS, Bayer, Clovis, Eisai, Exelixis, EMD Serono, Ely Lilly, Foundation One, Genentech, Janssen, Merck, Medivation, Novartis, Nektar, Pfizer, Pharmacyclics; Research funding to my institution: Astra Zeneca, Bavarian Nordic, Bristol Myers Squibb, Calithera, Celldex, Eisai, Exelixis, Genetech, GSK (glaxosmithkline), Immunomedics, Janssen, Medivation, Merck, New link Genetics, Novartis, Pfizer, Prometheus, Rexahn, Sanofi, Takeda, Tracon, Bayer, Clovis, EMD Serono, Ely Lilly, Janssen, Nektar. E Lin has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Tripathi A, Lin E, Agarwal N. Biomarkers in metastatic renal cell carcinoma in the era of immune checkpoint inhibitors. Ann Transl Med 2019;7(Suppl 6):S203. doi: 10.21037/atm.2019.07.13

