Editorial Commentary

Renal cell carcinoma response to checkpoint inhibitors may be predicted by senescence activity in tumor microenvironment

Javier González[1], Gaetano Ciancio[2]

[1]Servicio de Urología, Hospital General Universitario Gregorio Marañón, Madrid, Spain; [2]Department of Surgery and Urology, Miami Transplant Institute, University of Miami Miller School of Medicine, Jackson Memorial Hospital, Miami, FL, USA

Correspondence to: Gaetano Ciancio, MD. Department of Surgery and Urology, University of Miami Miller School of Medicine, Jackson Memorial Hospital, 1611 NW 12th Ave, Miami, FL 33136, USA. Email: gciancio@med.miami.edu.

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 May 21, 2019. Accepted for publication Jun 05, 2019.
doi: 10.21037/atm.2019.06.16
View this article at: http://dx.doi.org/10.21037/atm.2019.06.16

Renal cell carcinoma (RCC) represents a tailor's box composed of different forms of disease, each of them characterized by a complex relationship scenario established between the different actors involved (i.e., tumor cells, immune cells, and their respective expression products or tumoral microenvironment). This panorama favors a wide variety of biological behaviors (covering the spectrum between the slow-indolent to aggressive-invasive growth patterns) that are difficult to predict exclusively from a clinical standpoint (1).

Until recently, complete surgical removal of tumor burden was considered the only viable therapeutic option for these tumors, given that the standard radio- and chemotherapy protocols proved ineffective for RCC control. Therefore, surgical monotherapy only provided complete remissions in organ-confined tumors, while variable outcomes were obtained with this approach only in those cases in which lymphadenectomy, tumor thrombectomy, and/or metastasectomy completed primary tumor excision (1).

The efforts made during the 90s decade with different cytokines (i.e., beta-interferon, and interleukine-2) as therapeutic agents, opened the door to a new hope, thus improving overall survival in the subgroup of patients portending poor prognosis (late-stage disease). Recent advances in the understanding of RCC molecular pathogenesis have represented a formidable turning point in the development of a number of target inhibitors against vascular endothelial growth factor, tyrosine kinase, and mammalian target of rapamycin, which for instance have been shown effective to increase the chances of survival in the metastatic setting (1). Furthermore, the entry into the scene of the new immune checkpoint blockers (ICBs) has revolutionized the therapeutic armamentarium against advanced RCC showing additional progression-free and survival benefits, according to the outcomes provided by the CheckMate-214 randomized clinical trial (RCT) (2).

CheckMate-214 (2) is the first phase-III RCT to demonstrate the clinical effectiveness of a combination of ICBs in the first-line setting. The study compared the combination of ipilimumab + nivolumab (n=550) to sunitinib (n=546) in not previously treated intermediate- to high-risk International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) patients, trying to assess the objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) after treatment in each arm. Median OS was reached at 26 months, and the hazard ratio (HR) for death was 0.63 (99.8% CI, 0.44–0.89; P<0.001) favoring the ipilimumab + nivolumab combination. Median PFS by independent review was 11.6 versus 8.4 months (HR, 0.82; 99.1% CI, 0.64–1.05; P=0.03), and the ORR was 42% versus 27% (P≤0.001) (9% versus 1% for complete response) for the combination compared with Sunitinib, respectively.

Although promising, the candidate selection for ICBs remains a pending issue, given that the identification of the potential candidate still relies on the immuno-histochemical detection of certain biomarkers (i.e., PD-1/PD-L1) positivity in inflammatory cells within the tumor, that taken alone have been proved insufficiently reliable to anticipate a therapeutic response (3).

In this sense, Kamal *et al.* (4) have recently published a report trying to identify new markers that allow the anticipation of a positive response to immunotherapy in RCC. They utilized the existing large datasets from the Cancer Genome Atlas (TCGA) in an attempt to find predictors of disease aggressiveness in the tumor microenvironment (TME), hypothesizing that those predictors may influence the likelihood of responding to ICBs.

They found that metastatic RCCs (mRCCs) are inflamed compared to non-metastatic RCCs, demonstrating exuberant T-cell infiltration (CD4+ and CD8+) and increased expression of both immune checkpoints and activation markers (thus conferring aggressive biological potential) in RCC M+ tumors, in opposition to stronger macrophage, dendritic cell (DC), monocyte, and B-cell infiltrates in non-metastatic RCCs. Furthermore, they showed additional evidence on the different inflammation inducers and immune dysfunction encountered between M0 and M+ patients, by endorsing once again the association between CD4+ T-cell-2 (M0) and CD8+ T-cell-1 (M+) infiltration and poor survival despite prior treatment with ICBs, in opposition to active-DCs infiltration exhibiting improved overall survival rates following ICBs treatment.

Senescence (irreversible arrest of cell proliferation) along with anergy, stem-ness, and exhaustion are supposed to be the pathways leading to T-cell dysfunction in mRCC. Tumor senescent-cell cytokine secretion to TME (senescence-associated secretory phenotype or SASP) facilitates the recruitment of innate immune cells, promotion of premalignant tumor growth, and activation of hypoxic pathways which in turn increase the levels of a number of activation markers and immune checkpoints (TIGIT, CD38, CTLA-4, PDC1, PD-L1) favoring T-cell dysfunction. Therefore, senescence activity seems to play a major role in inducing tumor inflammation. In this way, the authors reported a hypothetical combined effect of tumor senescence and inflammation, potentially influencing the response to ICB therapy. They showed that mRCCs are highly senescent (with four out of eight senescence pathways enriched present in M+ tumors) when compared to M0 tumors. Therefore, they observed high oncogenic activity in M+ tumors, including a TP53 inactivation oncogenic pathway (increased senescence activity), thus suggesting that the tumor itself is senescent and not the surrounding immune cells. In addition, they highlighted that tumors exhibiting an increased expression of immunomodulatory molecules but low SENESCENCE TP53_TARGETS_UP enrichment were associated with poor response to ICB therapy, while tumors with both increased SENESCENCE TP53_TARGETS_UP enrichment and increase expression of immunomodulatory molecules were associated with good response to ICB therapy, meaning better intratumoral clearance of senescent cells. This clearance is dependent on CD4+ T-cell activity as well as activation of DCs via innate immunity cystolic DNA-sensors cyclic GMP-AMP synthase (cGAS), and stimulator of interferon genes (STING), which in turn promote antigen presentation to CD8+ cells.

In summary, Kamal *et al.* (4) proved that senescence activity alone is associated with poor survival in RCC, while senescence activity in individuals who receive ICBs therapy is associated with improved survival, suggesting that senescence coupled with activation of immunity via cGAS-STING signaling is predictive of ICB therapy response in RCC. With this report, the authors outlined a potential pathway that may help to explain the differences in response observed to ICBs therapy in RCC.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. González J, Gaynor JJ, Alameddine M, et al. Indications, complications, and outcomes following surgical management of locally advanced and metastatic renal cell carcinoma. Expert Rev Anticancer Ther 2018;18:237-50.
2. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378:1277-90.
3. Nunes-Xavier CE, Angulo JC, Pulido R, et al. A critical insight into the clinical transplantation of PD-1/PD-L1

blockade therapy in clear cell renal carcinoma. Curr Urol Rep 2019;20:1.
4. Kamal Y, Cheng C, Frost HR, et al. Predictors of disease aggressiveness influence outcome from immunotherapy treatment in renal clear cell carcinoma. Oncoimmunology 2018;16:8:e1500106.

Cite this article as: González J, Ciancio G. Renal cell carcinoma response to checkpoint inhibitors may be predicted by senescence activity in tumor microenvironment. Ann Transl Med 2019;7(Suppl 3):S139. doi: 10.21037/atm.2019.06.16

