Updates in the Management of Renal Cell Carcinoma

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Abstract

At JADPRO Live Virtual 2021, advanced practitioner experts reviewed clinical updates in the treatment of renal cell carcinoma, key patient counseling and monitoring considerations, and best practices to manage adverse events associated with therapies for renal cell carcinoma.

The most common kidney cancer, renal cell carcinoma is diagnosed in over 300,000 patients worldwide each year, including 74,000 patients in the US. Despite therapeutic advances, 5-year survival is still less than 12% for patients with metastatic disease.

During JADPRO Live Virtual 2021, Kirollos S. Hanna, PharmD, BCPS, BCOP, of M Health Fairview and the Mayo Clinic College of Medicine, and Zita D. Lim, PA-C, of MD Anderson Cancer Center, discussed clinical evidence supporting treatment options in kidney cancer and shared best practices for managing adverse events associated with available therapies.

BACKGROUND

As Ms. Lim explained, males are twice as likely as females to be diagnosed with renal cell carcinoma. Other common risk factors include familial syndromes, such as von Hippel-Lindau disease, hereditary papillary renal cell carcinoma, familial leiomyomas, and Birt-Hogg-Dubé syndrome. In addition, smoking increases the risk of diagnosis by 50% in males and 20% in females. Environmental exposure to benzenes, having advanced kidney cancer, and obesity have also been shown to increase the likelihood of developing renal cell carcinoma.

One of the first landmark studies for the disease was the COMPARZ trial, which randomized patients with metastatic renal cell carcinoma to front-line pazopanib vs. sunitinib (Motzer et al., 2013). The noninferiority trial comparing the two tyrosine kinase inhibitors showed that pazopanib was better tolerated than sunitinib in clear cell kidney cancer patients.

A major shift in therapy then occurred with the CheckMate 025 trial, which was the first study to use immunotherapy in kidney cancer (Motzer et al., 2015). Results of the study showed an overall survival advantage with the PD-1 inhibitor nivolumab (Opdivo) vs. everolimus

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among patients with previously treated advanced renal cell carcinoma.

"The data demonstrated very early separation of the curves with immunotherapy in these patients who had previously been treated with either sunitinib or pazopanib," said Ms. Lim. "We also learned that, unlike other tumors, PD-L1 expression does not play an important role in kidney cancer, so we don't have to use PD-L1 expression for stratification or treatment decisions."

The METEOR trial, which compared the VEGFR-targeted agent cabozantinib (Cabometyx) with everolimus in patients who had progressed on a previous tyrosine kinase inhibitor, also demonstrated improved progression-free survival, overall survival, and response rate for cabozantinib (Choueiri et al., 2015).

CURRENT IMMUNOTHERAPY OPTIONS

More recently, the CheckMate 214 trial demonstrated a clear survival benefit for combination immunotherapy in the front-line setting of advanced disease (Motzer et al., 2018). The phase III trial compared nivolumab plus ipilimumab (Yervoy) with sunitinib for previously untreated clear-cell advanced renal-cell carcinoma. Overall survival and objective response rates were significantly higher with nivolumab plus ipilimumab than with sunitinib among intermediate- and poor-risk patients with previously untreated disease.

In patients with favorable risk, overall survival benefit for either arm remains inconclusive even after 4 years of follow-up, while it was maintained in the intermediate- and poor-risk group (Albiges et al., 2020). Importantly, complete responses were seen in approximately 10% of patients with the combination, and there are patients who are being watched off therapy now.

"However, the doublet carries a high risk of autoimmune adverse events that requires expertise in management," said Ms. Lim.

The phase III KEYNOTE-426 trial randomized patients to a different combination (pembrolizumab [Keytruda] plus axitinib [Inlyta]) vs. sunitinib in the front-line setting of advanced renal cell carcinoma (Rini et al., 2019). Patients who received pembrolizumab plus axitinib, a tyrosine kinase inhibitor, had an objective response rate of 59% vs. 35.7% for sunitinib. With 30.6 months of follow-up, recently updated data showed that overall survival has still not been reached for the immunotherapy combination vs. 35.7% with sunitinib. Progression-free survival improved from 11.1 months on sunitinib to 15.4 months with the combination immunotherapy.

Ms. Lim noted, however, that safety data showed improved toxicity with combination nivolumab plus ipilimumab in terms of immune-related events.

Like the METEOR trial, the phase III CheckMate 9ER trial compared nivolumab plus cabozantinib to sunitinib but used a lower dose of cabozantinib to help with tolerability (Choueiri et al., 2021). The combination of nivolumab plus cabozantinib again demonstrated significant benefits over sunitinib with respect to progression-free survival, overall survival, and likelihood of response in patients with previously untreated advanced renal cell carcinoma.

Most recently, the CLEAR trial randomized lenvatinib (Lenvima) plus pembrolizumab, lenvatinib plus everolimus, or sunitinib in the front-line setting of advanced renal cell carcinoma (Motzer et al., 2021). According to Ms. Lim, the study demonstrated impressive data in favor of lenvatinib plus pembrolizumab, with a 71% objective response rate, which was "the highest seen in any trial so far."

RISK STRATIFICATION

Poor-Risk/Sarcomatoid

Poor-risk patients, especially those with sarcomatoid disease, should always be treated with nivolumab plus ipilimumab. According to Ms. Lim, these patients have an excellent response to the immunotherapy combination, including a 40% overall response rate. "Sarcomatoid RCC used to be a dreaded death sentence," said Ms. Lim. "Now, some of these patients can have an amazing response, even cures."

Intermediate Risk

There are many different approaches to patients with intermediate risk in the front-line setting, said Ms. Lim, because some cancers in this category are more aggressive than others. For patients with favorable sites of disease, options include tyrosine kinase inhibitor with or without immunotherapy,

single-agent immunotherapy, or even combination immunotherapy. Patients with aggressive intermediate-risk disease should be treated with nivolumab plus ipilimumab or combination tyrosine kinase inhibitor plus immunotherapy.

Good Risk

According to Ms. Lim, good-risk patients take the longest time to discuss because treatment is the most personalized. It's important to know your patient and the velocity of their cancer, she said. For very slow disease (i.e., late relapse oligo-metastatic lung, lymph node, or endocrine sites), the options include observation or local therapy (i.e., surgery, stereotactic body radiotherapy, and ablation). Conversely, good-risk patients with dangerous sites of disease should adopt a more aggressive treatment approach, including dual-agent immunotherapy or immunotherapy plus tyrosine kinase inhibitor.

IMMUNE-RELATED ADVERSE EVENTS

Immune checkpoint inhibitors introduce the potential for transformative, durable responses in multiple malignancies. Unfortunately, they also introduce the potential for toxicity (Figure 1). According to Dr. Hanna, activation of the immune system with these agents can "target" host tissues and organs, which can mimic (or flare) preexisting autoimmune conditions. The pathophysiology is not well understood, she said, but the treatment involves immunosuppressive agents.

"Although some side effects are more common than others, any inflammatory process that you could have could potentially manifest with immunotherapy," Dr. Hanna explained. "Importantly, combination immunotherapies, such as a PD-1 or PD-L1 inhibition plus CTLA-4 inhibition, can lead to an increase in the adverse event profile due to an overactivation of T cells."

Most patients with renal cell carcinoma who experience immune-related adverse events have either liver complications, endocrinopathies, gastrointestinal side effects, or skin reactions, which can be remembered with the acronym L-E-G-S.

According to Dr. Hanna, skin toxicities tend to manifest first, followed by gastrointestinal side effects (e.g., colitis or diarrhea). Endocrinopathies and transaminase elevations (e.g., alanine aminotransferase and aspartate aminotransferase) tend to manifest later. In fact, many of these adverse events can manifest one or two years into therapy.

"The majority of patients who experience an immune-related adverse event will do just fine, and these are frequently grade 1 or 2 adverse events," said Dr. Hanna. "However, serious immune-mediated adverse events can certainly manifest and can be fatal if not addressed urgently."

EDUCATIONAL PRINCIPLES

Before patients are initiated on an immune checkpoint inhibitor, underlying immune-related adverse events must be documented, especially for patients who have autoimmune conditions or autoimmune diseases at baseline.

"Autoimmune conditions are certainly not a contraindication for utilizing immune checkpoint inhibitors, but they are very important to note, especially in those patients who may be having a lot of breakthrough symptoms or side effects from their autoimmune condition," said Dr. Hanna.

Medication history and allergies are also important to document (e.g., if a patient is using chronic steroids for something outside of autoimmune diseases).

Another very important consideration for many patients is a wallet card. Having wallet cards on hand is going to be very important, said Dr. Hanna, especially if patients happen to be hospitalized away from their treatment facility. The wallet card helps identify potential complications or side effects that patients may experience, as not all institutions have access to electronic medical records.

Patients should also look out for certain signs and symptoms, including shortness of breath, rash, abnormal fatigue, muscle aches and pains, and weight loss. These symptoms should be communicated to the health-care team, which will then determine whether the symptom is immunotherapy related or caused by something else.

MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS

According to Dr. Hanna, corticosteroids remain the cornerstone of care for immune-related adverse events and resolve most of them. Mild skin reactions can be treated with topical steroids, while higher grade/persistent toxicity requires

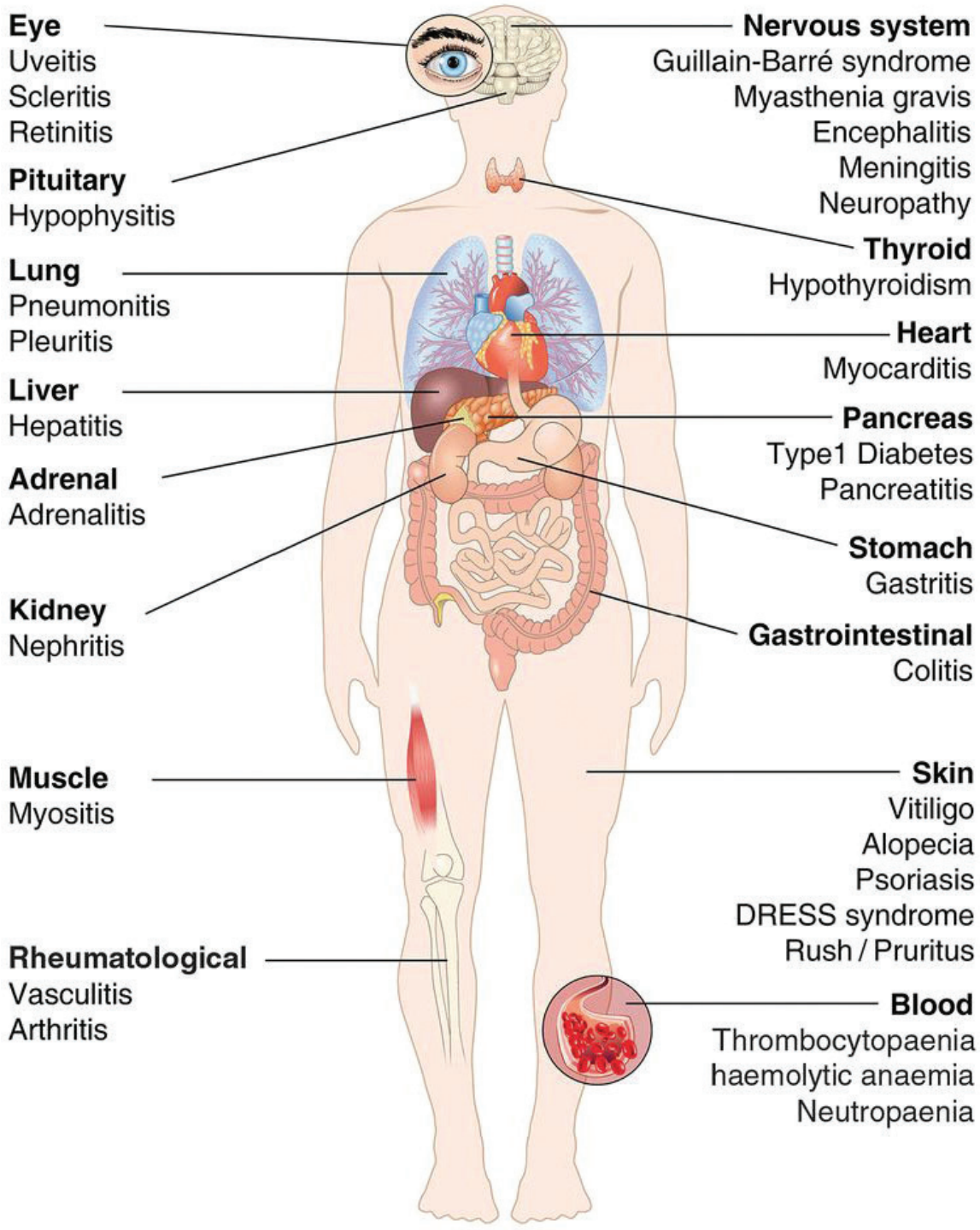

Figure 1. Some of the immune-related adverse effects (IRAEs) associated with checkpoints inhibitors in patients with cancer. DRESS = drug rash with eosinophilia and systemic symptoms. Republished from Varricchi et al. (2017), under the terms of a Creative Commons Attribution Non Commercial (CC By-NC 4.0) license.

systemic steroids. Oral steroids are preferred but may be administered intravenously when absorption is compromised (with colitis, for example).

For moderate cases (grade 2), immunotherapies are typically held and re-dosed if toxicity improves. Low-dose steroids are often used (prednisone 0.5-1 mg/kg/day).

Severe immune-related adverse events (grade 3 or 4) require high-dose steroids (prednisone 1-2 mg/kg/day) with a slow taper. Infliximab (5 mg/kg, once every 2 weeks) can also be used.

For endocrinopathies, hormone replacement therapy may be required.

In addition to immune-related adverse events, providers may also have to manage VEGF-related adverse events, which can be very different, said Dr. Hanna. VEGF-related adverse events include hypertension, proteinuria, and thromboembolic events, but there are sometimes overlapping toxicities, such as diarrhea, hypothyroidism, and liver function test elevation.

Disclosure

Dr. Hanna has served as a consultant/advisor for AbbVie, Amgen, Astellas Pharma, Inc., Bristol Myers Squibb, and Seattle Genetics. Ms. Lim has served on the speakers bureau for Exelixis, Inc.

References

Albiges, L., Tannir, N. M., Burotto, M., McDermott, D., Plimack, E. R., Barthelemy, P.,...Motzer, R. (2020).Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: Extended 4-year follow-up of the phase III CheckMate 214 trial. *ESMO Open, 5*(6), e001079. https://doi.org/10.1136/esmoopen-2020-001079

Choueiri, T. K., Escudier, B., Powles, T., Mainwaring, P. N., Rini, B. I., Donskov, F.,...Hessel, C. (2015). Cabozantinib versus everolimus in advanced renal-cell carcinoma. *New England Journal of Medicine*, *373*(19), 1814–1823. https://doi.org/10.1056/NEJMoa1510016

Choueiri, T. K., Powles, T., Burotto, M., Escudier, B., Bourlon, M. T., Zurawski, B.,...Pook, D. (2021). Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *New England Journal of Medicine*, *384*(9), 829–841. https://doi.org/10.1056/NEJMoa2026982

Motzer, R. J., Alekseev, B., Rha, S. Y., Porta, C., Eto, M., Powles, T.,... Kim, M. (2021). Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. *New England Journal of Medicine*, *384*(14), 1289–1300. https://doi.org/10.1056/NEJMoa2035716

Motzer, R. J., Escudier, B., McDermott, D. F., George, S., Hammers, H. J., Srinivas, S.,...Schutz, F. A. (2015). Nivolumab versus everolimus in advanced renal-cell carcinoma. *New England Journal of Medicine*, *373*(19), 1803–1813. https://doi.org/10.1056/NEJMoa1510665

Motzer, R. J., Hutson, T. E., Cella, D., Reeves, J., Hawkins, R., Guo, J.,...Choueiri, T. K. (2013). Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *New England Journal of Medicine*, *369*(8), 722–731. https://doi.org/10.1056/NEJMoa1303989

Motzer, R. J., Tannir, N. M., McDermott, D. F., Arén Frontera, O., Melichar, B., Choueiri, T. K.,...Bracarda, S. (2018). Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *New England Journal of Medicine, 378*(14), 1277–1290. https://doi.org/10.1056/NEJMoa1712126

Rini, B. I., Plimack, E. R., Stus, V., Gafanov, R., Hawkins, R., Nosov, D.,...Tartas, S. (2019). Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *New England Journal of Medicine*, *380*(12), 1116–1127. https://doi.org/10.1056/NEJMoa1816714

Varricchi, G., Galdiero, M. R., Marone, G., Criscuolo, G., Triassi, M., Bonaduce, D.,...Tocchetti, C. G. (2017). Cardiotoxicity of immune checkpoint inhibitors. *ESMO Open*, *2*(4), e000247. https://doi.org/10.1136/esmoopen-2017-000247