REVIEW Libri Oncol. 2017;45(2-3):55–59

IMMUNOTHERAPY OF RENAL CELL CARCINOMA

MARIJA MILETIĆ[1], MARIJANA JAZVIĆ[1], JASNA RADIĆ[1], MARIN PRPIĆ[1], BLANKA JAKŠIĆ[1] and ANTE BOLANČA[1,2]

[1]Clinical Department of Oncology and Nuclear Medicine, Sestre milosrdnice University Hospital Center, Zagreb, Croatia; [2]School of Denatal medicine, University of Zagreb, Zagreb, Croatia

Summary

Targeted therapy has been the standard of care for the treatment of metastatic renal cell carcinoma (mRCC). The current standard of care focuses on tyrosine kinase inhibitors (sunitinib, sorafenib, pazopanib, axitinib), antibodies to circulating VEGF receptor (bevacizumab) and m-TOR inhibitors (temsirolimus, everolimus). New immune-based therapies are emerging as a promising treatment for mRCC. Immune checkpoint blockade has shown clinically significant antitumor response. Monoclonal antibodies against immune checkpoint blockade molecules including PD-1 (programmed cell death 1) and CTLA-4 (cytotoxic T lymphocyte antigen 4) have become a major focus in the immune-based therapy since it has been reported that they have impressive antitumor effects.

The most studied inhibitors in the PD-1 pathway are: nivolumab, pembrolizumab and atezolizumab. Based on the results of the phase III clinical trial (CheckMate025) nivolumab, humanized monoclonal IgG4 antibody against PD-1, is the only agent that is approved by the FDA for the second-line treatment of mRCC. Ipilimumab is the first-in-class immunotherapeutic for blockade of CTLA-4. The immunotherapy combinations have demonstrated promising results in a randomized trials. The use of cancer treatment vaccines is another approach to immunotherapy and will be systematically evaluated in the future.

Immunotherapy has demonstrated great clinical potential and it represents crucial component of mRCC treatment. Developing immunotherapy to the point of clinical utility presents a number of issue and challenges, and more rigorous studies are needed.

KEY WORDS: *renal cell carcinoma, immunotherapy, checkpoint inhibition, vaccines.*

IMUNOTERAPIJA KARCINOMA BUBREGA

Sažetak

Ciljana terapija danas predstavlja osnovicu sistemskog liječenja metastatskog raka bubrega (mRB), a standard liječenja su tirozin-kinazni inhibitori (sunitinib, sorafenib, pazopanib, aksitinib), protutijela na cirkulirajući VEGF receptor (bevacizumab) i m-TOR inhibitori (temsirolimus, everolimus). Noviji imunoterapijski principi predstavljaju značajne iskorake u liječenju mRB. Jedna forma imunoterapije je inhibicija imunoloških kontrolnih točaka (eng. immune checkpoint). Blokiranjem jednog od dva najistraživanija imunološka receptora; antigen 4 povezan s aktivnošću citotoksičnih T-limfocita (CTLA-4) i receptor programirane stanične smrti (PD-1), potenciramo antitumorski imunološki odgovor.

Među najistraživanije anti-PD-1 inhibitore ubrajamo: nivolumab, pembrolizumab i avelumab. Nivolumab je ljudsko monoklonalno antitijelo kojega je Američka agencija za hranu i lijekove odobrila u drugoj liniji liječenje mRB, a na osnovi rezultata kliničke studije faze III (CheckMate025). Ipilimumab je prvi registrirani checkpoint inhibitor koji blokira inhibitorni signal (CTLA-4 receptor) na površini citotoksičnih T limfocita. Veliki pomak u imunoterapiji mRB postigut je primjenom konkomitantnih protokola liječenja. Novija istraživanja primjene imunoterapije u liječenju raka bubrega uključuju i pronalaženje cjepiva koje bi prepoznavalo i uništavalo promijenjene tumorske stanice.

Imunoterapija ima jasno mjesto i veliki potencijal u liječenju raka bubrega. Ipak, postoji još niz problema i pitanja te su potrebna brojna daljnja istraživanja kako bi se iskoristio njen puni potencijal.

KLJUČNE RIJEČI: *karcinom bubrega, imunoterapija, inhibicija imunoloških kontrolnih točaka, cjepiva.*

INTRODUCTION

Worldwide, the incidence of renal cell carcinoma (RCC) has steadily increased over the last two decades. In 2014 the Croatian National Cancer Registry stated 731 new cases of RCC diagnosed in Croatia (1). About one quarter of patients will present with metastatic disease at the time of diagnosis, and another quarter will develop metastatic disease despite complete surgical removal of the primary tumor (2). Clear cell RCC is the most prevalent histologic subtype being assigned to 70–80% of all RCC patients (2).

Advanced and metastatic RCC (mRCC) is highly lethal tumor with a poor prognosis. Since RCC is highly resistant to chemotherapy, three major categories of systemic drugs are currently being used as first-line treatment of metastatic disease: drugs that target the vascular endothelial growth factor (VEGF) pathway (inhibitors of tyrosine kinase - sunitinib, sorafenib, pazopanib, axitinib, tivozanib cabozantinib; the monoclonal antibody against VEGF receptor - bevacizumab), drugs that target the mTOR pathway (mTOR inhibitors - temsirolimus, everolimus) and immune-based therapies (3).

IMMUNOTHERAPY

Renal cell carcinoma represents an immunosensitive tumor due to high levels of tumor infiltrating immune cells, including lymphocytes, macrophages and dendritic cells (2). Multiple different mechanisms of immunosuppression are preventing immune cells from exercising their antitumor activities. These mechanisms are being intensively investigated in hope of finding therapeutically safe and effective inhibitors able to counteract tumor-induced immunosuppression.

More than two decades, unspecific immunotherapy using cytokines, interleukin-2 (IL-2) and interferon-α (IFNα), had been the mainstay for management of advanced disease.

IFNα as the first biologics to be evaluated in the mRCC setting (4). It has anti-proliferative and immune stimulatory activity. On the other hand it is a difficult drug to use because of the chronic administration as well as the severity and chronicity of side effects and it is inferior to most of the newer agents. Based on the results of several phase III trials, which suggest that greatest therapeutic potential of IFNα may be realized in combination with other biological response modifiers, it is currently approved as a treatment for patients with mRCC in combination with bevacizumab (5,6).

High-dose bolus IL-2 (HD IL-2) was approved by the Food and Drug Administration (FDA) in 1992 for the treatment of mRCC due to the potential for durable complete responses (7%) in a small number of patients, but the toxicity of HD IL-2 therapy, in particular, make it a poor standard therapy (7). Despite many limitations, this treatment modality remains valuable therapeutic option for eligible patients and should be considered in the treatment algorithm at centers with adequate experience.

Although many factors have limited its generalized use, the succes of its application serves us as proof of principle that immunotherapies can eliminate tumor cells in some patients, encouraging efforts to develop better tolerated and more effective immunotherapy regimens.

CHECKPOINT INHIBITION

Numerous studies have begun to discover the multiple mechanisms by which renal cancer cells can avoid being attacked by the immune system, and recently, monoclonal antibodies against immune checkpoint blockade molecules including PD-1 (programmed cell death 1) and CTLA-4 (cytotoxic T lymphocyte antigen 4) have become a major focus in the immune-based therapy (8).

Programmed cell death 1 molecule is expressed on the surface of activated T cells, and interaction between PD-1 and its ligands, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), leads to T cell inactivation. Anti-PD-1 antibodies (nivolumab, pem-

brolizumab, atezolizumab and avelumab) can bind to the PD-1 receptor, blocking its interaction with PD-L1/L2 to prevent T cell inactivation (9).

In the randomized, open-label, phase III controlled trial (CheckMate025), nivolumab (a monoclonal IgG4 antibody against PD-1) was compared with everolimus in patients with mRCC who received prior treatment (10). The study demonstrated an overall survival (OS) benefit of nivolumab compared with everolimus (25.0 months versus 19.6 months) following progression on first-line treatment (inhibitors of tyrosine kinase). Safety analyses showed that 19% of the patients receiving nivolumab experienced grade 3/4 treatment-related adverse events (AE) versus 37% for those receiving everolimus. The most common AE experienced by patients in the nivolumab group was fatigue (in 2% of the patients). Based on that, in 2015, the FDA approved nivolumab for advanced RCC in the second-line setting. Following this approval, various anti-PD-1 antibodies are actively being investigated for use in mRCC (11,12,13).

Early studies (CheckMate016, CheckMate214) suggest that combination therapy of checkpoint inhibitors with targeted therapy, even combination therapy of dual immune checkpoint inhibition (CTLA-4 plus PD-1) may potentially provide additional clinical benefit not seen with either modality alone (14,15).

Fully humanized, engineered monoclonal antibody against PD-L1 protein, atezolizumab, was initially approved for the treatment of patients with advanced urothelial cancer (16). In a global, multicentre, open-label, randomised phase II study (IMmotion150) 305 patients with previously untreated, locally advanced or mRCC were randomly assigned to atezolizumab plus bevacizumab, atezolizumab alone or sunitinib alone. An analysis of results found that patients whose cancer expressed PD-L1 and were treated with atezolizumab plus bevacizumab had improvement in progression-free survival (PFS) compared to those who were treated with sunitinib alone (14.7 vs 7.8 months) (17). Frequency of all-grade treatment-related AE were similar between arms. The results from ongoing phase III study (IMmotion151) will help to confirm clinical benefit of combined therapy with atezolizumab and bevacizumab in patients with RCC (18).

Ipilimumab, a fully humanized anti-CTLA-4 antibody, is approved by the FDA for the treatment of advanced melanoma (19). It has been investigated in combination with nivolumab in mRCC (the nivolumab–ipilimumab arm of CheckMate016) (20). Full doses of nivolumab and ipilimumab were not tolerated, but nivolumab with reduced dose ipilimumab was reasonably well tolerated. These should be further evaluated, particularly in the context of dose and schedule modification and combination therapy.

The CheckMate214 study compares the combination of nivolumab plus ipilimumab to sunitinib monotherapy in patients with previously untreated mRCC. The study will provide valuable information on the optimal initial treatment approach for patients with all-risk groupings of mRCC. Further trials investigating ipilimumab alone and in combination with other drugs are ongoing (21,22).

Based on their mechanism of action, checkpoint inhibitors are associated with select AE, toxicities that have an autoimmune etiology and require specific management strategies. The most common and typically earliest onset adverse reaction include dermatologic toxicity in the form of rash and pruritus, gastrointestinal AE in the form of diarrhea and colitis, hepatotoxicity, endocrinopathy in the form of hypophysitis and hypothyroidism, pneumonitis and renal insufficiency (23). Treatment-related immune AE are predominantly grade 1 or 2 in severity, and can be managed by holding or discontinuing the checkpoint inhibitors and administering high-dose corticosteroids followed by other immune modulatory agents if side effects are not quickly controlled (24). If identified early, they are almost always reversible, but if they go unrecognized, these events can lead to significant morbidity, even death. Compared to drugs that target PD-1, serious AE seem to be more likely with antibody against CTLA-4.

VACCINES

The use of cancer treatment vaccines is another approach to immunotherapy. The role of vaccine target antigens, target delivery and immune stimulants will have to be systematically evaluated in the future. In contrast to other cytotoxic therapies, cancer vaccines have demonstrated minimal toxicity in all clinical trials that have been reported to date.

The clinical translation of cancer vaccines into efficacious therapies has been challenging for several decades with mixed results. In April 2010, the FDA approved the first therapeutic cancer vaccine, sipuleucel-T, an autologous immune cell prostate cancer vaccine (25).

Due to recent advances in research, therapeutic vaccines are steadily gaining ground as promising treatment modalitie against RCC, especially when they are given in combination with other forms of cancer therapy (26).

The multipeptide vaccine IMA901, based on 9 tumor-associated peptides, has recently been assessed in a phase III clinical trial. In this trial, patients with mRCC were randomized to receive either sunitinib with IMA901 or sunitinib alone as first-line treatment (27). The study demonstrate no survival advantage to the addition of IMA901 to sunitinib versus sunitinib alone, while the randomized phase II trial demonstrated a clear association of a clinical benefit in mRCC patients with an immunological response to the administered synthetic tumor-associated peptide (28).

Dendritic cell-based vaccine (AGS-003) for RCC is being investigated in combination with well-established targeted drug therapies (sunitinib) in a clinical trial phase III (ADAPT) (29).

Early results showed that the combination of AGS-003 and sunitinib can potentially maximize immune response in patients, with a goal of adding little to no toxicity (30). Further studies allowing for assessment of survival advantage related to AGS-003 are anticipated. However, the true benefit for cancer vaccines may be in the adjuvant setting.

CONCLUSION

Significant increase in the understanding of the biology of RCC has resulted in notable achievements in treatment options. Complete and durable unmaintained remissions are rare with agents that target VEGF or mTOR pathway, which differs from the small percentage of patients reaching complete remissions with high-dose IL-2-based immunotherapy.

A new class of immunotherapy agents, immune checkpoint inhibitors, has ushered in a new era in the treatment of patients with mRCC. Early results from some current trials are extremely encouraging and will likely lead to more indications in addition to the approved indications for the treatment of mRCC. While the efficacy of these new therapies is enhanced, the toxicity is less severe than that seen with other treatment modalities. The toxicities from checkpoint immunotherapy represent a new class of adverse events, manageable with early application of systemic corticosteroids or immunomodulators.

Therapeutic cancer vaccines of different forms are being actively evaluated in the clinic. A better understanding of host-tumor interactions and tumor immune escape mechanisms are required to develop effective cancer vaccines.

Optimal sequencing, investigating biomarkers and other factors predictive of response and resistance to immunotherapy and evaluating the combination of different treatment modalities (immunotherapy with targeted therapy, or multiple immune-modulators) become even more important in order to select patients with the greatest chance of durable disease control and survival.

REFERENCES

1. The Croatian National Cancer Registry (2014)
2. Liu KG, Gupta S, Goel S. Immunotherapy: Incorporation in the evolving paradigm of renal cancer management and future prospects. Oncotarget. 2017;8(10): 17313–17327.
3. Greef B, Eisen T. Medical treatment of renal cancer: new horizons. Br J Cancer. 2016;115(5):505–516.
4. Choudhury M, Efros M, Mittelman A. Interferons and interleukins in metastatic renal cell carcinoma. Urology. 1993;41(1):67–72.
5. Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet. 2007;370(9605):2103–11.
6. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Archer L, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J Clin Oncol. 2010;28(13): 2137–43.
7. Rosenberg SA, Yang JC, Topalian SL. Treatment of 283 consecutive patients with metastatic melanoma or renal cell cancer using high-dose bolus interleukin 2. JAMA. 1994;271:907–913.
8. Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res. 2005;65:1089–1096.

9. Viteri S, González-Cao M, Barrón F, Riso A, Rosell R. Results of clinical trials with anti-programmed death 1/programmed death ligand 1 inhibitors in lung cancer. Translational Lung Cancer Research. 2015;4(6): 756-762.
10. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. The New England journal of medicine. 2015;373(19):1803–1813.
11. ClinicalTrials.gov (NCT02619253). A Phase I/Ib, Open Label, Dose Finding Study to Evaluate Safety, Pharmacodynamics and Efficacy of Pembrolizumab (MK-3475) in Combination With Vorinostat in Patients With Advanced Renal or Urothelial Cell Carcinoma.
12. McDermott DF, Sosman JA, Sznol M, Massard C, Gordon MS, Hamid O, et al. Atezolizumab, an Anti-Programmed Death-Ligand 1 Antibody, in Metastatic Renal Cell Carcinoma: Long-Term Safety, Clinical Activity, and Immune Correlates From a Phase Ia Study. Journal of clinical oncology. 2016;34(8):833–842.
13. ClinicalTrials.gov (NCT01984242). A Phase II, Randomized Study of Atezolizumab Administered as Monotherapy or In Combination With Bevacizumab Versus Sunitinib In Patients With Untreated Advanced Renal Cell Carcinoma.
14. ClinicalTrials.gov (NCT01472081). A Phase I Study of Nivolumab (BMS-936558) Plus Sunitinib, Pazopanib or Ipilimumab in Subjects With Metastatic Renal Cell Carcinoma.
15. ClinicalTrials.gov (NCT02231749). A Phase III, Randomized, Open-Label Study of Nivolumab Combined With Ipilimumab Versus Sunitinib Monotherapy in Subjects With Previously Untreated, Advanced or Metastatic Renal Cell Carcinoma.
16. Ning YM, Suzman D, Maher VE, Zhang L, Tang S, Ricks T, et al. FDA Approval Summary: Atezolizumab for the Treatment of Patients with Progressive Advanced Urothelial Carcinoma after Platinum-Containing Chemotherapy. The Oncologist. 2017;22:1–8.
17. McDermott DF, Atkins MB, Motzer RJ, Brian IR, Escudier BJ, Fong L, et al. A phase II study of atezolizumab (atezo) with or without bevacizumab (bev) versus sunitinib (sun) in untreated metastatic renal cell carcinoma (mRCC) patients (pts). J Clin Oncol. 2017;6:431.
18. ClinicalTrials.gov (NCT02420821). A Phase III, Open-Label, Randomized Study of Atezolizumab in Combination With Bevacizumab Versus Sunitinib in Patients With Untreated Advance Renal Cell Carcinoma [IMmotion151].
19. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363:711–23.
20. Hammers HJ, Plimack ER, Infante JR, Rini BI, McDermott DF, Ernstoff MS, et al. Expanded cohort results from CheckMate016: a phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC). J Clin Oncol. 2015;33.
21. Grosso JF, Jure-Kunkel MN. CTLA-4 blockade in tumor models: an overview of preclinical and translational research. Cancer immunity. 2013;13:5.
22. ClinicalTrials.gov (NCT02381314). A Phase I, Open-Label, Dose Escalation Study of MGA271 in Combination With Ipilimumab in Patients With B7-H3-Expressing Melanoma, Squamous Cell Cancer of the Head and Neck, Non Small Cell Lung Cancer, and Other B7H3 Expressing Cancers.
23. Villadolid J, Amin A. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. Transl Lung Cancer Res. 2015; 4(5): 560–575.
24. Postow MA. Managing immune checkpoint-blocking antibody side effects. American Society of Clinical Oncology educational book / ASCO American Society of Clinical Oncology Meeting. 2015:76–83.
25. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363,411–422.
26. Amato RJ, Hawkins RE, Kaufman HL, Thompson JA, Tomczak P, Szczylik C, et al. Vaccination of metastatic renal cancer patients with MVA-5T4: a randomized, double-blind, placebo-controlled phase III study. Clinical cancer research: an official journal of the American Association for Cancer Research. 2010;16:5539–5547.
27. Rini IB, Stenzl A, Zdrojowy R, Kogan M, Shkolnik M, Oudard S, et al. IMA901, a multipeptide cancer vaccine, plus sunitinib versus sunitinib alone, as first-line therapy for advanced or metastatic renal cell carcinoma (IMPRINT): a multicentre, open-label, randomised, controlled, phase III trial. The Lancet Oncology. 2016;17(10):1599-1611.
28. Walter S, Weinschenk T, Stenzl A, Zdrojowy R, Pluzanska A, Szczylik C, et al. Multipeptide immune response to cancer vaccine IMA901 after single-dose cyclophosphamide associates with longer patient survival. Nat Med. 2012;18(8):1254-61.
29. An International Phase III Randomized Trial of Autologous Dendritic Cell Immunotherapy (AGS-003) Plus Standard Treatment of Advanced Renal Cell Carcinoma (ADAPT) Available athttp://www.clinicaltrials.gov.
30. Figlin RA, Nicolette CA, Amin A, et al. Monitoring T-cell responses in a phase II study of AGS-003, an autologous dendritic cell-based therapy in patients with newly diagnosed advanced stage renal cell carcinoma in combination with sunitinib. J Clin Oncol. 2011;29:2532.

Corresponding author: Marija Miletić, Clinical Department of Oncology and Nuclear Medicine, Sestre milosrdnice University Hospital Center, Vinogradska cesta 29, Zagreb, Croatia; e-mail: mmileti90@gmail.com