The Past, Present, and Future of Renal Cell Carcinoma Treatment: A Systematic Review

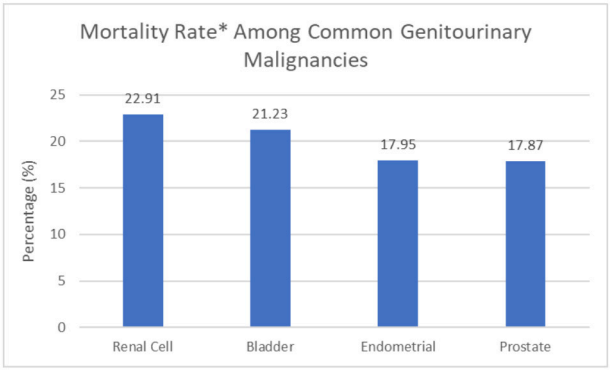
by Nityam Rathi

Abstract: Renal cell carcinoma is a malignancy of the kidney, and is among the most common and lethal cancers affecting the genitourinary tract in males and females. As the kidneys play a critical role in maintaining homeostasis in an organism (particularly by regulating excretion and reabsorption of solutes, influencing hormone release, and maintaining blood pressure), malignancies of these organs have several complex side effects. The most common genetic deficiency observed in renal cell carcinoma is inactivation or mutation of the von Hippel-Lindau (VHL) tumor suppressor gene, which is critical for hypoxia-induced angiogenesis and has generated several hypotheses on how to treat the malignancy. After the initial surgery or radiation to the localized disease, systemic pharmacological agents are utilized to prolong survival once the cancer has metastasized. The aim of this review is to present the evolution of pharmacological agents in managing renal cell carcinoma. In its three main sections, this review will explore cytokine immunotherapies utilized in the 1990s, vascular endothelial growth factor-tyrosine kinase inhibitor (VEGF-TKIs) systemic therapies devised in the 2000s, and finally treatment with targeted immunotherapies. With the rapid pace of pharmaceutical development, the prognosis for renal cell carcinoma continues to improve.

Introduction

Renal cell carcinoma is a malignancy of the kidney and is among the most common cancers affecting the genitourinary tract in males and females. While much progress has been made in the management and diagnosis of renal cell carcinoma, it remains one of the most lethal cancers, giving rise to more than 140,000 cancer-related deaths yearly (Capitanio et al., 2019). Among the most common genitourinary malignancies (including renal cell, bladder, prostate, and endometrial cancers), renal cell carcinoma has the greatest mortality rate (Figure 1) (American Cancer Society, 2018). Because the kidneys play a critical role in maintaining homeostasis in an organism—particularly by regulating excretion and reabsorption of solutes, influencing hormone release, and maintaining blood pressure—malignancies of these organs have several complex side effects. The hallmarks of kidney cancer include blood in the urine, chronic pain in the back, fever, fatigue, and ultimately death from metastasis. Common sites of metastasis include the lungs, bones, lymph nodes, liver, adrenal glands, and brain (Bianchi et al., 2012); as such, treating this cancer early on may prevent failure of other necessary organ systems. Over the last 30 years, the treatment landscape for renal cell carcinoma has changed drastically, as more has been learned about its development and progression.

Renal cell carcinoma can be inherited or sporadic. Patients who inherit mutations that give rise to renal cell carcinoma typically begin demonstrating



*Mortality Rate is calculated by:
Mortality Rate=(Estimated Deaths)/(Estimated New Cases)

Figure 1: Mortality rates among common genitourinary malignancies. Renal cell carcinoma has the greatest mortality rate (nearly 23%) among the common genitourinary cancers, followed by bladder cancer (approximately 21%), endometrial cancer (approximately 18%), and prostate cancer (nearly 18%). Figure is based on "Cancer Facts & Figures 2018" (American Cancer Society, 2018).

numerous cancerous nodules in the kidney at around age 37, while the more common sporadic renal cell carcinoma presents as a solitary tumor at around age 61 (Pavlovich et al., 2003). Regardless of the age of onset or etiology pattern, the most common genetic deficiency observed in renal cell carcinoma is inactivation or mutation of the von Hippel-Lindau (VHL) tumor suppressor gene (Latif et al., 1993). The protein encoded by the VHL gene has numerous functions, but its role in angiogenesis (the creation of new blood vessels) in response to hypoxia has generated several hypotheses on how to treat the malignancy. The question that I seek to answer is: how have the elucidation of the angiogenesis pathway and other discoveries on its pathology changed the treatment of renal cell carcinoma?

Whereas radiation and/or nephrectomy were the only defenses in the past, modern management of the cancer is more comprehensive. After the initial surgery or radiation—depending on whether the disease presents as metastasized or not—systemic pharmacological agents are utilized to prolong survival for both familial and sporadic cases of renal cell carcinoma. The aim of this review is to present the evolution of pharmacological agents in managing renal cell carcinoma. In its three main sections, this review will explore cytokine immunotherapies utilized in the 1990s, vascular endothelial growth factor-tyrosine kinase inhibitor (VEGF-TKIs) systemic therapies devised in the 2000s, and finally treatment with targeted immunotherapies. With the rapid pace of pharmaceutical development, the prognosis for renal cell carcinoma continues to improve.

1990s: The Age of Cytokine Immunotherapies

Between 1900 and 1987, sporadic cases of spontaneous regression of renal cell carcinoma were detected in patients who were simultaneously experiencing bacterial infections (Challis & Stam, 1989). Clinicians hypothesized that such cases, although rare, may have arisen due to the activation of the patients' immune system in response to the bacterial infection. Such hypotheses led to the labeling of renal cell carcinoma as "immunogenic." Once engaged to combat the bacterial infection, the immune system likely discovered the cancerous cells in the body and generated an immune response that ultimately induced cancer regression. Scientists and clinicians subsequently tested this hypothesis by developing cytokine immunotherapies. In general, cytokine immunotherapies generate a widespread activation of immune cells in the body, such as B cells, T cells, and macrophages, that ultimately target the cancer.

By the early 1990s, cytokine immunotherapies were primarily used in the post-surgery and/or metastatic renal cell carcinoma setting with the goal of reducing the intensity of the cancer. Two of the most significant drugs developed were synthetic High Dose-Interleukin 2 (HD-IL2), and Interferon alfa-2α, often denoted as IFN-α in the clinic. Mechanistically, these two therapies differ. HD-IL2 induces the proliferation of immune cells and stimulates these cells to target the cancer, while IFN-α makes tumor cells more immunogenic. In murine models, a combination of HD-IL2 and IFN-α was found to be correlated with anti-tumor activity (Brunda et al., 1987).

To assess whether the same would hold in metastatic renal cell carcinoma patients, a phase II clinical trial was devised to compare survival and toxicities in patients treated with HD-IL2 alone or with the HD-IL2/IFN-α combination (Atkins et al., 1993). Atkins et al. (1993) hypothesized that, given unequivocal evidence of anti-tumor activity of the HD-IL2/IFN-α combination in *in vivo* studies, similar trends would be seen in humans. In the phase II trial, Atkins et al. included 99 patients with metastatic renal cell carcinoma. 28 patients were administered the combination HD-IL2/IFN-α treatment, and 71 patients were administered HD-IL2 treatment alone. Researchers then followed up with all patients for 26 months to track survival, encountered toxicities, and response.

It was found that, although median survival rates were nearly equal for the HD-IL2 and HD-IL2/IFN-α arms (Figure 2; 15.5 months vs. 16 months, respectively), response rates were higher for the HD-IL2 arm (17% vs. 11%, respectively). Furthermore, differences in toxicity were observed. Significantly more neutropenia (low white blood cell count) and myocarditis/ischemia (reduced blood supply to the heart) were noted on the HD-IL2/IFN-α arm, while serum bilirubin was significantly elevated (an indicator of liver damage) in patients on the HD-IL2 arm. Nevertheless, improved response rates with

HD-IL2 therapy, in comparison with other cytokine immunotherapies, were observed in additional phase II trials (Fyfe et al., 1995).

In the broader context of renal cell carcinoma treatment, this phase II trial led by Atkins et al. showed that cytokine immunotherapies confer a survival benefit to metastatic renal cell carcinoma patients. Unlike the findings in murine models, therapy with HD-IL2 alone was found to produce meaningful and durable responses with manageable and reversible toxicity in renal cell carcinoma patients. A possible reason for the differences in outcomes of the two arms is that the HD-IL2/IFN-α arm may have over-activated the immune system. An excessive number of activated immune cells (such as B cells, T cells, and macrophages) may lead to scenarios of autoimmunity, in which the immune system erroneously identifies normal cells in organs as dangerous, and subsequently attacks them. Although cytokine immunotherapy was approved by the FDA for treatment of renal cell carcinoma in 1992, the need for more specific, targeted therapies to reduce toxicities and further improve survival was established.

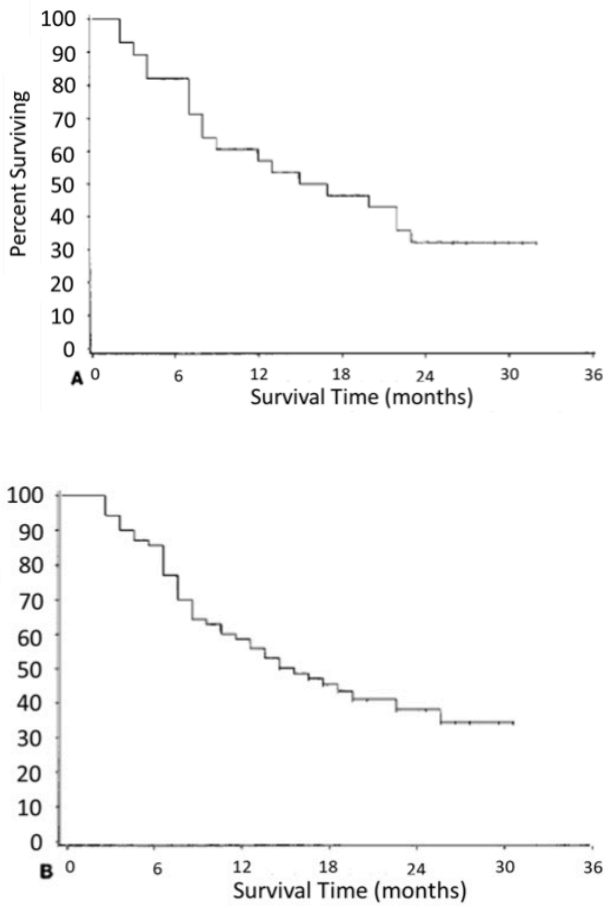


Figure 2: Response to different cytokine immunotherapy treatment regimens in renal cell carcinoma. Patients were given either (a) a combination of HD-IL2 and IFN-α (n=28), or (b) HD-IL2 exclusively (n=71) via bolus intravenous injection every 8 hours, days 1 to 5 and 15 to 19. HD-IL2 was given at a dosage of 0.8 mg/m^2 and IFN-α at a dosage of 3 x 10(6) U/m^2 in the combination arm, and HD-IL2 was given at a dosage of 1.33 mg/m^2 when given as a monotherapy.
A) Survival conferred with the HD-IL2/IFN-α combination treatment. Mortality rate at 24 months is approximately 70%. B) Survival conferred with the HD-IL2 single treatment. Mortality rate at 24 months is approximately 70%. (Figure adapted from Atkins et al., 1993.)

2003-Present: Sunitinib and Other Targeted, Pathway-Specific VEGF-TKI Therapies

While the pathogenesis of kidney cancer is quite complex, mutations in the *VHL* gene are known to play a role in cellular physiology by upregulating the expression of the vascular endothelial growth factor (VEGF) gene. The protein encoded by VEGF plays a critical role in forming blood vessels that carry nutrient-rich blood to the site of the tumor. Ultimately, this leads to tumor growth and provides an escape path for malignant cells, which increases the probability of metastasis. The angiogenesis pathway is initiated by the binding of VEGF to the VEGF Receptor (VEGFR), which conducts the signal via tyrosine-kinase activity. In all, there are three VEGFR to which the VEGF ligand can bind: VEGFR-1, VEGFR-2, and VEGFR-3. Ligand-receptor binding can result in one or more of three critical outcomes that yield angiogenesis: endothelial cell migration (the lining up of endothelial cells to form a blood vessel), a change in vascular permeability (the capacity of blood vessel to allow entry of nutrients to enrich the blood), and endothelial cell proliferation (the replication of endothelial cells that will ultimately line the blood vessel) (Morabito et al. 2006). Upon discovery of VHL mutations and their consequences for the angiogenesis pathway, the novel idea of targeting such a specific cellular pathway with synthetic chemicals in hopes of mitigating cancer growth became popular.

Blocking angiogenesis with inhibitory pharmacological agents (known as VEGF-Tyrosine Kinase Inhibitors, VEGF-TKIs) revolutionized the

treatment of renal cell carcinoma. Drugs of this class include Sunitinib, Cabozantinib, Sorafenib, and Axitinib, among others (Figure 3), and each drug inhibits unique component(s) of the angiogenesis pathway. In mouse xenograft models, Sunitinib was found to reduce tumor microvessel density, confirming the drug's potential to reduce angiogenesis and inhibit tumor growth (Mendel et al., 2003).

To assess whether Sunitinib could further improve survival benefits offered by cytokine immunotherapies in renal cell carcinoma, a phase III multicenter clinical trial was formulated. This trial compared progression-free survival (PFS)—the time between treatment initiation and observation of cancer progression—in patients treated with Sunitinib or IFN-α (Motzer et al., 2007). Given pre-clinical evidence of Sunitinib's anti-angiogenic properties and preliminary clinical data, Motzer et al. hypothesized that Sunitinib would yield superior outcomes when compared with IFN-α. In the phase III trial, Motzer et al. included 750 patients with metastatic renal cell carcinoma randomized in a 1:1 ratio to the Sunitinib or IFN-α treatment arms. Patients in both groups continued treatment until the occurrence of disease progression.

It was found that PFS was significantly higher for the group treated with Sunitinib as compared to IFN-α (11 months vs. 5 months, respectively; Figure 4). Furthermore, a greater percentage of patients treated with IFN-α had to discontinue treatment due to secondary medical consequences of the drug as compared to those treated with Sunitinib (13% vs. 8%, respectively). However, the incidence of certain toxicities was greater in the Sunitinib arm than the IFN-α arm. 6.4% of patients on the Sunitinib arm experienced hypertension, as compared to 0.3% on the IFN-α arm, and 14.1% of patients on the Sunitinib arm experienced diarrhea, as compared to 3.3% on the IFN-α arm. Similar findings of enhanced survival, coupled with cardiovascular toxicities during treatment with VEGF-TKIs have been noted in subsequent clinical studies (Schmidinger et al., 2008; Catino et al., 2018).

The development of VEGF-TKIs was a major landmark in renal cell carcinoma treatment. The phase III trial led by Motzer et al. showed that targeted inhibition of the angiogenesis pathway with Sunitinib could improve PFS and quality-of-life in patients with metastatic renal cell carcinoma. Yet, the upsurge of cardiovascular toxicities became of concern when prescribing Sunitinib. It is known that the same VEGF pathway is used by healthy cells, such as those in the cardiovascular system, to receive

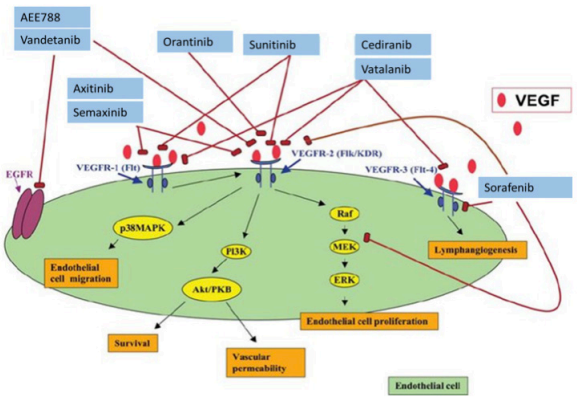


Figure 3: Targets of different VEGF-TKI therapies. Although VEGF-TKIs achieve the same result of preventing angiogenesis, each drug has a different specificity. Of the diverse TKIs shown above, Sunitinib, Axitinib, and Sorafenib are more widely utilized in treatment of renal cell carcinoma. Sunitinib and Axitinib each preferentially target both VEGFR-1 and VEGFR-2, and Sorafenib targets VEGFR-2 and MEK. Figure modified from Morabito et al., 2006.

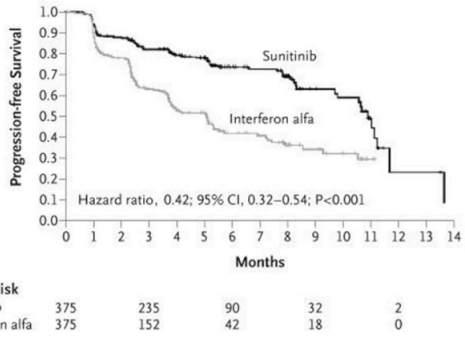


Figure 4: Progression-Free Survival (PFS) is Greater in Patients Treated with Sunitinib than IFN-α. A total of 750 patients were randomized in a 1:1 ratio to either the Sunitinib treatment arm or the IFN-α arm. Sunitinib was administered orally at a dose of 50 mg once daily, taken without regard to meals, in 6-week cycles consisting of 4 weeks of treatment followed by 2 weeks without treatment. IFN-α was administered subcutaneously three times per week on nonconsecutive days at 3 MU per dose during the first week, 6 MU per dose the second week, and 9 MU per dose thereafter. PFS conferred with the Sunitinib treatment was approximately 11 months, while PFS conferred with the IFN-α treatment was approximately 5 months (Motzer et al., 2007).

nutrients from blood. Renal cell carcinoma patients who present with poor cardiovascular health are often administered Sunitinib in combination with drugs that moderate hypertension. If cardiovascular health is to the point that the safety of the patient would be compromised with VEGF-TKIs, Sunitinib is forgone completely. Nevertheless, the efficacy of Sunitinib in improving survival outcomes led to its establishment as a first-line of therapy for renal cell carcinoma in the post-surgery or radiation setting. The revolutionary paradigm of targeted, pathway-specific cancer therapies has since been explored in the immunological context.

2009-Present & Future: Targeted Immunotherapies: Stimulating the Immune System at a More Refined Level

In an attempt to offer further lines of treatment for metastatic renal cell carcinoma patients, investigators revisited the idea of renal cell carcinoma as "immunogenic" with the paradigm of targeted therapies. In 2004, it was first reported that T cells, particularly cytotoxic T cells, could be isolated in higher levels from patients with regressing metastatic kidney cancer (Takahashi et al., 2004). Subsequent studies revealed that increased expression of PD-L1 (Programmed-Death Ligand 1) molecules on the cell surface of cancer cells over time is associated with a poor prognosis in renal cell carcinoma patients because PD-L1 binds to the PD-1 (Programmed Death Protein-1) receptors on the T cell, thereby inhibiting the T cell-mediated immune response (Thompson et al., 2006). By inducing death of the T cells, cancer cells could evade the host immune system. Together, these two discoveries created the basis for the clinical use of targeted immunotherapies that would block the PD-L1/PD-1 interaction, thereby stimulating the T cell-mediated immune response against cancerous cells in a more specific manner as compared to previous cytokine immunotherapies.

Since 2009, two novel targeted immunotherapies have entered clinical trials. The first is Nivolumab, an immune checkpoint inhibitor antibody that blocks the Programmed Death-1 (PD-1) receptor found on T cells, thereby preventing the PD-1/PD-L1 interaction that results in death of the T cell. The second is Ipilimumab, a T-cell potentiator that works by blocking cytotoxic T-lymphocyte antigen-4 (CTLA-4), a receptor on the T cell that inhibits stimulatory signaling upon binding to its ligand. Effectively, both therapies remove inhibitory signals and promote antitumor activity (Figure 5). A small phase I clinical trial showed that metastatic renal cell carcinoma patients treated with Nivolumab experienced manageable toxicities and durable responses that, in some cases, persisted after drug discontinuation (McDermott et al., 2015). Although not used as a monotherapy for renal cell carcinoma, Ipilimumab led to improved survival outcomes as compared to those treated with standard-of-care glycoprotein peptide vaccine treatment (10.0 months vs. 6.4 months) in metastatic melanoma patients (Hodi et al., 2010). Success of both of these treatments as monotherapies led to the hypothesis that these two drugs may have a synergistic effect when used in combination (Melero et al., 2015).

In the CheckMate 0214 trial, a phase III clinical trial, approximately 850 intermediate or poor-risk renal cell carcinoma patients were enrolled and

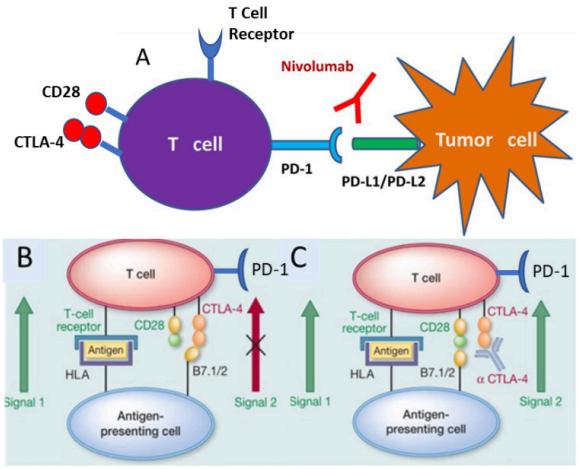


Figure 5: Nivolumab and Ipilimumab mechanism of action. A) Nivolumab is an antibody that binds to the PD-1. While PD-1 normally binds Programmed Death-Ligand 1 (PD-L1) expressed on tumor cells, ultimately resulting in death of the T cell, Nivolumab binds with greater affinity, thereby preventing death of the T cell (Guo et al., 2017). B) Full activation of the T cell involves binding of the antigen from the Antigen-presenting cell (left) and binding of co-receptor CD28 with a receptor (B7) on the Antigen-presenting cell. Normally, the second receptor on the Antigen-Presenting cell (B7) binds to CTLA-4, thereby hindering T cell activation. C) Ipilimumab (denoted as α CTLA-4) binds to the CTLA-4 receptor on the T cell, inducing full activation of the T cell. B and C are adapted from Lipson & Drake, 2011.

randomized to one of two treatment arms: Nivolumab and Ipilimumab (425 patients), or Sunitinib (422 patients) (Motzer et al., 2018). Researchers followed up with these patients to track overall survival and progression-free survival to compare the efficacies of the different treatment arms.

It was observed that patients on the Nivolumab + Ipilimumab arm had superior survival outcomes than patients on the Sunitinib arm (Figure 6). Patients treated with the Nivolumab + Ipilimumab combination had a greater duration of overall survival (Not Reached vs. 26.0 months, respectively) and progression-free survival (11.6 months vs. 8.4 months) than those treated with Sunitinib.

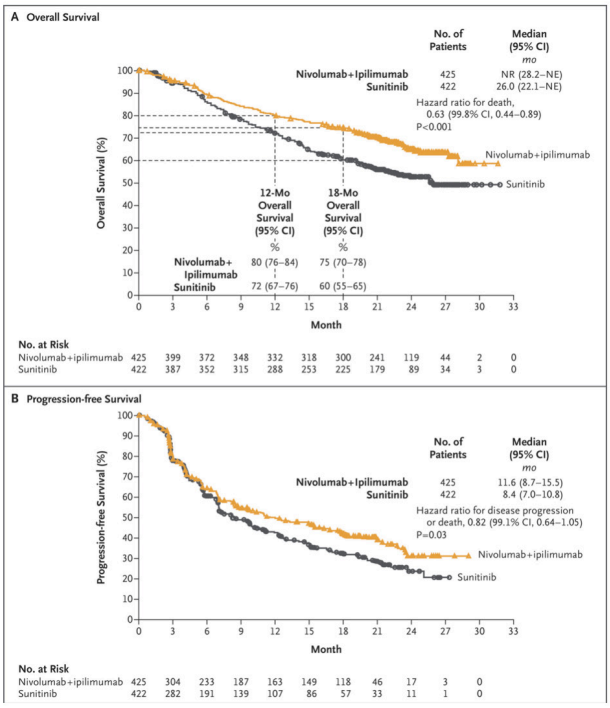


Figure 6: Overall Survival and Progression-Free Survival is greater for patients treated with Nivolumab + Ipilimumab than with Sunitinib. A) Overall Survival is determined by calculating percentage of patients who have survived at a given time point (i.e: 12 months, as demarcated above) after initiating a treatment. Advanced renal cell carcinoma patients who received Nivolumab and Ipilimumab demonstrated much higher survival rates than those who were treated with Sunitinib at any given time point. B) Progression-free Survival is determined by calculating percentage of patients who are not only surviving on a treatment, but also do not demonstrate any signs of worsening disease at a given time point. Advanced renal cell carcinoma patients who received Nivolumab and Ipilimumab demonstrated longer progression-free survival than those who were treated with Sunitinib (Motzer et al., 2018).

Cardiovascular toxicities and other severe adverse events were significantly lower for the Nivolumab + Ipilimumab arm as compared to the Sunitinib arm. These findings provide support for the use of Nivolumab and Ipilimumab as a first-line of therapy for metastatic renal cell carcinoma.

The phase III trial led by Motzer et al. has helped establish combination immunotherapy as a new approach to treating renal cell carcinoma. Stimulating the immune system more specifically than previous cytokine immunotherapies has reduced many of the side effects previously observed with cytokine immunotherapies, which induce extensive activation of the immune system. Current efforts are geared toward evaluating the implications of treatment regimens, which include a combination of targeted immunotherapies and VEGF-TKIs to assess whether cross-talk between the drug actions may modulate toxicities previously observed with VEGF-TKIs (National Cancer Institute, 2018). Additionally, in an attempt to develop personalized treatment regimens, researchers are exploring gene expression levels, primarily of proteins found in the tumor microenvironment that may be predictive of adverse or positive responses to immune checkpoint inhibitors (Zhu et al., 2019).

Conclusion

Over the last thirty years, our ability to treat patients with advanced renal cell carcinoma has greatly improved. Whereas nephrectomy and/or radiation were once the only options available and were only sufficient to eradicate the cancer if detected early enough, it soon became clear that the use of pharmacological agents would be needed to manage more aggressive renal cell carcinoma.

The 1990s saw an upsurge in the use of cytokine immunotherapies, such as HD-IL2 and IFN-α, which activated various cells of the human immune system. Despite improving survival of metastatic renal cell carcinoma patients, treatment with HD-IL2 and/or IFN-α often led to severe side effects as a result of an overactive immune system. Upon elucidation of key molecular pathways involved in the onset and progression of renal cell carcinoma, the early 2000s were characterized by the use of pathway-specific VEGF-TKIs such as Sunitinib. These drugs prevented cancer cells from receiving nutrients from the blood supply, but also adversely affected healthy cells, given that both use the

same angiogenesis pathway. Nevertheless, the survival rates were unequivocally superior to those observed in cytokine immunotherapies, which led to the FDA-approval of VEGF-TKIs as a first line of treatment in the post-surgical and radiation setting. Recent pharmacological research has applied the concept of pathway-specific cancer therapies in developing targeted immunotherapies (Nivolumab and Ipilimumab) since the late 2000s. Targeted immunotherapies are devoted to activating the patient's immune system in a more specific manner (as compared to cytokine immunotherapies) by blocking the PD-1/PD-L1 interaction that inhibits the immune response against cancer. The ongoing CheckMate 0214 trial has shown that combining Nivolumab and Ipilimumab yields even better survival outcomes than VEGF-TKIs, indicating that immunotherapy agents may be superior in managing renal cell carcinoma.

With the accumulation of several treatment options for renal cell carcinoma, we have entered into an exciting era of developing personalized treatment regimens for different cohorts of patients. Can we predict who will respond well to immunotherapies? Does combining immunotherapies with other types of anti-cancer drugs confer even better survival outcomes? As the findings from new clinical trials are published, the treatment and management of renal cell carcinoma will continue to evolve.

References

American Cancer Society. (2018, April 27). *Cancer facts & figures 2018*. https://www.cancer.org/content/dam/.../2018/cancer-facts-and-figures-2018.pdf

Atkins, M. B., Sparano, J., Fisher, R. I., Weiss, G. R., Margolin, K. A., Fink, K. I.... Gucalp R. (1993). Randomized phase II trial of high-dose interleukin-2 either alone or in combination with interferon alfa-2b in advanced renal cell carcinoma. *Journal of Clinical Oncology, 11*(4), 661-670.

Bianchi, M., Sun, M., Jeldres, C., Shariat, S. F., Trinh, Q. D., Briganti, A. . . . Karakiewicz, P. I. (2012). Distribution of metastatic sites in renal cell carcinoma: A population-based analysis. *Annals of Oncology, 23*(4), 973-980.

Brunda, M. J., Bellantoni, D., & Sulich, V. (1987). In vivo anti tumor activity of combinations of interferon alpha and interleukin-2 in a murine model. Correlation of efficacy with the induction of cytotoxic cells resembling natural killer cells. *International Journal of Cancer, 40*(3), 365-371.

Capitanio, U., Bensalah, K., Bex, A., Boorjian, S., Bray, F., Coleman, J., . . . Russo, P. (2019). Epidemiology of renal cell carcinoma. *European Urology, 75*(1), 74-84.

Catino, A. B., Hubbard, R. A., Chirinos, J. C., Townsend, R. M., Keefe, S., Haas, N., . . . Ky, B. (2018). Longitudinal assessment of vascular function with sunitinib in patients with metastatic renal cell carcinoma. *Circulation: Heart Failure, 11*(3), E004408.

Challis, G., & Stam, H. (1990). The spontaneous regression of cancer. A review of cases from 1900 to 1987. *Acta Oncologica (Stockholm, Sweden), 29*(5), 545-550.

Fyfe, G., Fisher, R. I., Rosenburg, S. A., Sznol, M., Parkinson, D. R., & Louie, A. C. (1995). Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *Journal of Clinical Oncology, 13*(3), 688-696.

Hodi, F., O'Day, S., Mcdermott, D., Weber, R., Sosman, J., Haanen, J., . . . Lebbé, C. (2010). Improved survival with ipilimumab in patients with metastatic melanoma. *The New England Journal of Medicine, 363*(8), 711-723.

Latif, F., Tory, K., Gnarra, J., Yao, M., Duh, F. M., Orcutt, M. L.. . . Lerman, M. I. (1993). Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science, 260*(5112), 1317-1320.

Mcdermott, D., Drake, C., Sznol, M., Choueiri, T., Powderly, J., Smith, D., . . . Atkins, M. (2015). Survival, durable response, and long-term safety in patients with previously treated advanced renal cell carcinoma receiving nivolumab. *Journal of Clinical Oncology, 33*(18), 2013-20.

Melero, I., Berman, D., Aznar, M., Korman, A., Gracia, J., & Haanen, J. (2015). Evolving synergistic combinations of targeted immunotherapies to combat cancer. *Nature Reviews Cancer, 15*(8), 457-472.

Mendel, D., Laird, A., Xin, X., Louie, S., Christensen, J., Li, G., . . . Cherrington, J. (2003). In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: Determination of a pharmacokinetic/pharmacodynamic relationship. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research, 9*(1), 327-337.

Morabito, A., De Maio, E., Di Maio, M., Normanno, N., & Perrone, F. (2006). Tyrosine kinase inhibitors of vascular endothelial growth factor receptors in clinical trials: Current status and future directions. *Oncologist, 11*(7), 753-764.

Motzer, R., Hutson, T., Tomczak, P., Michaelson, M., Bukowski, R., Rixe, O., . . . Figlin, R. (2007). Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *The New England Journal of Medicine, 356*(2), 115-124.

Motzer, R., Tannir, N., Mcdermott, D., Arén Frontera, O., Melichar, B., Choueiri, T., . . . Hawkins, R. (2018). Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *The New England Journal of Medicine, 378*(14), 1277-1290.

National Cancer Institute. (2018, January 23). *Axitinib and Nivolumab in treating participants with unresectable or metastatic TFE/translocation renal cell carcinoma* (Clinicaltrials.gov Identifier NCT03595124). https://clinicaltrials.gov/ct2/show/NCT03595124.

Pavlovich, C. P., Schmidt, L. S., & Phillips, J. L. (2003). The genetic basis of renal cell carcinoma. *Urologic Clinics of North America, 30*(3), 437-454, vii.

Schmidinger, M., Zielinski, C. C., Vogl, U. M., Bojic, A., Bojic, M., Schukro, C., . . . Schmidinger, H. (2008). Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. *Journal of Clinical Oncology, 26*(32), 5204-5212.

Takahashi, Y., Mena, O., Srinivasan, R., Igarashi, T., Lundqvist, A., Suffredini, D.… Childs, R. (2004). Cd8+ T-cells specifically cytotoxic to renal cell carcinoma (RCC) cells can be isolated from patients with regressing metastatic kidney cancer after allogeneic nonmyeloablative hematopoietic cell transplantation (NMHCT). *Blood, 104*(11), 4984.

Thompson, R., Kuntz, S., Leibovich, B., Dong, H., Lohse, C., Webster, W., . . . Kwon, E. (2006). Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. *Cancer Research, 66*(7), 3381-3385.

Zhu, J., Pabla, S., Labriola, M., Gupta, R. T., McCall, S., George, D. J.… Zhang. T. (2019). Evaluation of tumor microenvironment and biomarkers of immune checkpoint inhibitor (ICI) response in metastatic renal cell carcinoma (mRCC). *Journal of Clinical Oncology, 37*(8 suppl), 607.