Recent Updates in Treatment of Renal Cell Carcinoma – A Comprehensive Review

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ABSTRACT

The incidence and prevalence of Renal cell carcinoma (RCC) continues to grow making it the 7th and 8th most common cancer among men and women in the U.S. respectively. Loss or mutation of VHL (Von-Hippael Lindau) gene is yet known major cause of the development of RCC. This mutation or loss of VHL gene causes increased expression and production of hypoxia-inducible factors and various other pro-angiogenic growth factors following which the neoangiogenes occurs ultimately causing the development of cancer. RCC is a unique malignancy as it considerably causes host immune dysfunction. Multimodality paradigm of treatment of metastatic RCC broadly includes surgical approaches and adjuvant therapy. Anti-cancer market has seen the emergence of other neoadjuvant approaches like the targeted therapy and has prolonged the survival in the past years. The evidence of the reduced effectiveness gained from the cytokines where the primary tumor did not respond well and the spontaneous regression of metastases following nephrectomy drew attention on the use of targeted VEGF (TKI) therapy. These drugs induce tumor shrinkage by blocking the angiogenesis of the tumor cells. Pre-operative treatment with targeted therapy can affect the overall quality of life by reducing tumor bulk prior to surgery. Such an intervention can save the patient from invasive surgical approaches and render unresectable disease as "resectable'**.** Sunitinib has now become a first line therapy. Biologics like monoclonal antibodies are also showing therapeutic effectiveness. Axitinib being the 2nd line drug has been approved for the treatment after failure of 1st line sunitinib therapy. Other mechanisms like m TOR inhibition being used as 3rd line therapy and are an active area of health service research. This review highlights the recent updates in the palliation and treatment modalities of advanced RCC and the emergence of various checkpoint inhibitors as potential future trends for the treatment.

Key Words: *Nephrectomy, cytoreduction, immunotherapy, VEGF therapy.*

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INTRODUCTION

Cancer is a group of disease that became a major issue with increased carcinogenic exposure that raises cancer incidences [1]. Among them Renal carcinoma is the fourteenth most common cancer worldwide [2] and Renal cell carcinoma is most common (approx 85%) among all types of renal carcinomas. The etiologic factor for RCC is yet unknown but there may be several other acquired risk factors that may be associated with the development of RCC like tobacco, obesity, hypertension, occupational exposure to various harmful chemicals, analgesic abuse and other renal diseases. There are some other factors which may or may not be associated with development of RCC like alcohol, tea, hormone and radiation [3]. The occurrence of RCC increases and garner increased attention as new biological and therapeutic details unfold from this indeterminate cancer. The body is remarkably good at hiding the symptoms and so people with the RCC have an advanced disease by the time it is discovered. The landscape for the RCC treatment has changed dramatically in the recent years with the addition of three new FDA approved agents for RCC. The disease may remain clinically occult for most of its course and only 10% of patients may present the classical triad of symptoms – Haematuria, Flank pain and a palpable mass in the abdomen [4]**.** This review mainly highlights the recent advances in the treatment of RCC and also target check point inhibitors for RCC treatment.

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PATHOPHYSIOLOGY

Genetic basis of the disease

Recent advances in the biology of RCC include increased demonstration of VHL-associated molecular features. VHL is an autosomal dominant gene and is inactivated in up to 80% of the sporadic cases of RCC by deletion, mutation and methylation. Inactivation of the VHL gene causes the build-up of HIFs leading to the activation of multiple genes like VEGFR and PGDFR. The resulting persistent stimulation may promote tumor angiogenesis, tumor growth and metastases [4].

Metabolic basis of Disease

Naturally, the VHL gene encodes for the ubiquitin ligase enzyme that targets HIFs by forming a complex. Ubiquitin mediated degradation of HIFs is an oxygen sensing process. In normoxia, HIF propyl hydroxylase (PHD) hydroxylates HIF thereby enabling VHL complex and ubiquitin ligase to degrade HIF. In hypoxia, PHD does not hydroxylate HIF, hence the VHL complex and ubiquitin ligase is not able to degrade HIF due to which the HIF accumulates and being the transcription factor of the hypoxia responsive genes such as VEGF, PDGF it ultimately leads to the over expression of VEGF and PDGF [4, 5].

Treatment Modalities

The therapeutic approach to renal cell carcinoma (RCC) is mediated by the probability of cure, which is associated directly with the stage or degree of tumor dissemination. More than 50% of patients with early stage renal cell carcinoma are cured, but the outcome for stage IV disease is poor.

The principal treatment options for renal cell cancer are as follows:

- Surgery
- Radiation therapy
- Immunotherapy
- Molecular-targeted therapy

Surgical Treatment

Surgical resection has been the only known significant cure for localized tumors. Partial or radical nephrectomy may be utilized, depending on tumor burden and patient's overall characteristics. Open, laparoscopic, or robotic surgical techniques may become potential future trends.

a) Partial Nephrectomy

Partial Nephrectomy of the cancer tissue is a favorable option for patients with chronic kidney disease [6]. For a T1a renal mass, the 2017 National Comprehensive Cancer Network (NCCN) guideline recommends partial nephrectomy, stating that radical nephrectomy should not be used when nephron-sparing procedures are possible. For clinical T1b tumors, the NCCN guideline states that the standard of care is either radical nephrectomy or partial nephrectomy (when possible) [7].

According to the 2009, American Urology Association (AUA) management guideline, in patients with a T1 renal mass, complete surgical excision by partial nephrectomy is a standard of care. The guideline recommends discussing the potential advantages of nephron-sparing surgery with the patient, such as avoidance of dialysis and reduced risk of chronic kidney disease. If partial nephrectomy is not technically feasible, then radical nephrectomy should be considered as an alternate standard of care [5].

b) Radical nephrectomy

Radical nephrectomy, the most commonly preferred standard surgical procedure for treatment of localized RCC. It involves complete removal of the Gerota fascia and its contents, perirenal fat, ipsilateral adrenal gland, with or without ipsilateral lymph node dissection. Radical nephrectomy provides a better surgical impact and margin because the local kidney tissues which are spared in partial nephrectomy may get involved in forming further tumors. Approximately 20-30% of patients with clinically localized disease develop metastatic disease after nephrectomy. Some surgeons believe that the adrenal gland should not be removed due to the low probability of ipsilateral adrenal metastasis and the morbidity related to adrenalectomy [6].

The NCCN guideline states that patients with enlarged lymph nodes (palpable or visible or detected on preoperative imaging) should undergo lymph node dissection [2].

Cytoreduction by Radiofrequency thermal ablation

Ablation techniques including radiofrequency ablation (RFA) and cryoablation have been shown to influence the immune system in animal models by causing local tissue destruction. Radiotherapy is used for palliation-not actually curing the disease but just decreasing the violence of disease. Thermal ablation refers to the destruction procedures that uses extreme of temperature to cause local tissue damage [8]. It introduces a metal probe into a tumor using direct visual or imaging guidance with either ultrasound or computed tomography (CT) to destruct the tumor. Using two temperature extremes causing either burning (RFA) or freezing (cryoablation), small tumors can be effectively destructed. Cryo-ablation for the localized treatment and has been shown to be safe and effective in treating kidney, liver, bone, lung, adrenal and soft tissue masses. It induces membrane disruption, solution effects, organelle disruption, ice crystallization, and microvascular thrombosis Freezing procedures are palliative because they cause a local analgesic effect. Cryo-probe destructs cells by varying degrees depending upon its proximity with the cancer tissue causing either necrotic cell death or apoptosis [9].

The AUA guideline panel cautions that larger tumors (>3.5 cm) and those with uneven shape or infiltrative appearance may be linked with increased risk of recurrence when managed with thermal ablation [2].

- **Limitations of Radiation Therapy**

RCC is traditionally considered to be a radio-resistant tumor and had seldom shown any in vitro or clinical response in patients when given in the adjuvant settings. It does not have a significant role in curing the disease in the adjuvant setting, but is effective for palliation and control of distant sites of metastasis particularly to bone and brain but then during the radiation therapy the patient has to stop any other standard therapy for curing the disease which can lead to further progression of the disease [9, 10].

Adjunctive Therapy

Cytokine-based therapies have demonstrated lack of improvement over surgical treatment. So the attention is being focused on the adjuvant use of VEGF receptor tyrosine kinase inhibitor (TKI) therapy [11, 12].

Neoadjuvant Therapy

This therapy induces initial tumor shrinkage and it should be determined whether the implementation of pre-operative treatment can reduce tumor bulk prior to surgery. It reduces the severity of the invasive surgical approaches and render unresectable disease "resectable" thereby controlling the systemic disease prior to removal of the primary mass.

- **VEGF pathway inhibition**
  - **Sunitinib**

Sunitinib, the current standard of care for first line therapy for patients with good or intermediate risk RCC. Sunitinib is a small molecule inhibitor of multiple tyrosine kinases including VEGFR and PDGFR, insulin like growth factor receptor and fibroblast growth factor receptor-1 tyrosine kinase. Reported toxicities are fatigue, nausea, diarrhea, stomatitis and cardio toxicity. Patients with pre-existing hypertension and coronary heart disease are at greatest risk of cardiotoxicity. Studies reported that the administration of high dose IL-2 after sunitinib failure has demonstrated a high incidence of cardiac toxicity. Quality of life is significantly better in the sunitinib group of patients than the IFN-a or IL-2 group. These findings ultimately established sunitinib as the first line therapy for advanced RCC. Sunitinib is still being investigated in combination with other agents [11, 12].

- **Pazopanib**

It has shown partial responses in some patients while in some it has shown stable disease. Common adverse effects include-diarrhea, cutaneous manifestations and hypertension [9].

- **Sorafenib**

Sorafenib is a multi-kinase inhibitor of tumor cell proliferation and angiogenesis. It has activity against multiple tyrosine kinases including (VEGFR 1, 2, 3), (PDGFR-a,b) ,Stem cell growth factor receptor(c-kit).It is the first approved drug for the treatment of advanced RCC after the of Interleukin-2.Studies reported that the median progression free survival and the effectiveness is significantly higher in patients with cytokine-refractory mRCC when treated with sorafenib than placebo. Sorafenib was compared to IFN-□ in patients who were not previously exposed to any drug and it was found that there was no significant difference in progression free survival between sorafenib and IFN-□ which concludes that there is still a confusion for oncologists regarding prioritizing these two treatments as 3rd line, but the cost and high level of expertise for administering immunotherapy is high enough to be easily accepted by patients and even after considerable research, the results obtained cannot be generalized to clearly declare one treatment more effective than other. Studies have been reinforced to know how to rationally utilize sorafenib in advanced RCC. The role of sorafenib in patients refractory to other anti-VEGF therapy is also not clear.

With this advent of the new treatments 'exposure and experience it is becoming more clear to the researchers what has to be still explored about the treatment modalities so that controversies like the disease resistance, disease control issues, management of toxicities and detrimental long term complications can be figured out. Toxicity management is the need of the hour and has to be aggressively maintained. Toxicity and tolerability issues impede the patient's overall quality of life and in most cases patient compliance.

- **mTOR pathway inhibition**

Target of rapamycin (TOR) is a highly conserved serine/threonine kinase that adjusts cell growth and metabolism in response to nutrients, growth factors, cellular energy, and stress. Finding mTOR resulted in a basic change in the perspective about cell growth which is highly regulated, plastic process controlled by TOR-dependent signaling pathways. TOR is known in two structurally and functionally different multiprotein complexes, TORC1 and TORC2. Both of them like the TOR itself, are highly conserved. Mammalian TORC1 (mTORC1) is rapamycin sensitive and regulates temporal cell growth by altering several cellular processes, such as translation, transcription, ribosome biogenesis, nutrient transport, and autophagy. mTORC2 is rapamycin insensitive and mediates spatial cell growth by adjusting the actin cytoskeleton. Therefore, the two TOR complexes collectively regulate the fundamental cell growth process. As a central regulator of cell growth, TOR has significant

role in development and aging and has been implicated in disorders such as cancer, cardiovascular disease, obesity, and diabetes. The major mTOR inhibitors in the market are temsirolimus and everolimus. Temsirolimus has been a prior treatment for patients with poor risk disease and as third line for patients developing refractory disease after the failure of the first and second line therapy as it caused improvement in the overall survival demonstrating a doubling of progression free survival in patients Thus, the mTOR pathway provides an option of switching drug classes when different treatments become refractory and disease is known to progress [11, 12].

- **Temsirolimus**

Temsirolimus was approved by USFDA in 2007. It is a highly specific inhibitor of m TOR and is the central regulator of intracellular signaling pathways involved in tumor cell growth, proliferation and angiogenesis. It demonstrated improved progression free survival, overall survival and significantly disease stabilization when compared to the conventional immunotherapy Toxicities include fatigue, nausea, dyspnea and rash. Temsirolimus showed a survival benefit in intermediate to poor risk patients with advanced RCC [11].

- **Everolimus**

Everolimus was approved by USFDA in 2009 as an inhibitor of mTOR. Studies have shown significant difference in patients receiving everolimus being the second or third line therapy. Its combinations with sorafenib and bevacizumab (first anti-angiogenesis drug to hit the market) are also exhibiting significant therapeutic effect and tolerability [11, 12].

- **Monoclonal antibodies**

The monoclonal antibodies recognize a tumor-associated antigen specific for RCC. Bevacizumab is the first humanized monoclonal antibody that was approved in 2004 by USFDA, inhibits tumor angiogenesis by targeting all major forms of VEGF. Bevacizumab targets VEGF which led to higher median progression free survival and objective response rate hence proved the concept that the VEGF signaling pathway is important for the progression of RCC in humans. Studies show that bevacizumab therapy can be a feasible treatment option in presurgical patients. Studies are ongoing to evaluate its efficacy with other therapeutic agents including IL-2, sorafenib, sunitinib, temsirolimus and erlotinib [11]. Its discovery has shifted the standard protocol of the RCC treatment from highly complicated immune therapy to the specific targeted therapy with lesser side effects [11-13].

- **Novel approach-G250**

It is a chimerical monoclonal antibody directed against carbonic anhydrase-9, a unique heat sensitive surface antigen which is ubiquitously over expressed in RCC. Studies to explore its effectiveness in the patients are currently underway [11].

Role of immunotherapy in RCC

- **High dose IL-2**

High dose interleukin-2 and interferon were the most commonly administered therapies before the recent introduction of targeted agents. Immunotherapy hit the market after having obtained the understanding of the immune dysfunction which occurs in RCC making it a unique malignancy. The tumor immunity is impaired due to deregulation in the proliferation of regulator-T cells and myeloid derived suppressor T cells. RCC cells have receptors for B7-H1 and B7-H4 which upon binding with their receptors act as negative regulators of T-cell mediated immunity making the primary tumor an "immunosuppressive sink. The optimal sequencing of immunotherapy and targeted therapy still remains confusing. Amongst these therapy biologics like IL-2 pose a higher risk of cardiotoxicity than cytokines. Nevertheless, IL-2 remains the only significant therapeutic modality to have shown proven durable responses. Further the administration of IL-2 is another challenge which has limited its widespread use historically. A high degree of expertise is required in patient selection and administration and should be administered in an intensive care type of setting with close evaluation before every dose. Despite of all, this therapy is still recommended as the third line due to the necessity to have at least four lines of treatment because in most cases tumors develop resistance to the ongoing therapy (that targets a particular pathway of disease development). Patients with excellent organ function, minimal co morbidity and good performance status can be only given this therapy. Studies are ongoing on IL-2 combination.

- **Interferon**

Historically, Interferon was the standard frontline option in the treatment of metastatic RCC as it had shown clinical benefit which was followed by the trials where it became the standard comparator in first line trials. Since improved progression free survival was seen in case of targeted therapy, use of interferon was largely replaced by targeted therapy. Interferon and bevacizumab combination had shown comparable efficacy to targeted agent but the toxicity profile was significant leading to its higher-dropout rates in trials [14].

Sunitinib versus Interferon-alpha in metastatic RCC

The median PFS and objective response rate is significantly longer in the sunitinib group than in IFN-a group. Treatment related fatigue is higher in the IFN-agroup whereas diarrhoea is more common in the sunitinib group. However, patients in the sunitinib group have

reported a better quality of life than patients in the IFN-a group [15].

Second line therapy-Axitinib in the treatment of renal cell carcinoma

Axitinib is a potent selective second generation inhibitor of VEGFR1, 2, 3 and PDGF; and colony stimulating factor-1 receptor tyrosine kinase. Axitinib is 50-450 times more potent that the first generation VEGFR inhibitors. The most common side effects are hand foot syndrome, fatigue, hypertension, dyspnea, and diarrhea. Phase 3 RCT compared axitinib to sorafenib in patients with metastatic RCC who had progressed despite first line therapy and a statistically significant advantage was found for axitinib over sorafenib for the progression free survival. Axitinib has been approved for the treatment of advanced RCC after failure of one systemic first line therapy. AXIS is the first trial to have demonstrated that the effect of axitinib is less pronounced with 1st line sunitinib and more pronounced with 1st line cytokines. However, in the real world scenario the post-cytokine cohort of patients is disappearing rapidly as the targeted agents are becoming increasingly available worldwide. As a 2nd line both everolimus and axitinib have shown significant benefit in patients. Both everolimus and axitinib are potent drugs in this patient population and the ideal sequencing of drugs in the second line setting can only be determined by a head to head comparison between these agents [16]. Studies have also been conducted where three different pathways were targeted at once using combination of Lenavatinib which targets VEGF and FDGF and everolimus which targets m TOR. Researchers obtained improved median progression free survival of 14.6 months which led to its approval. Cabozatinib is a dual VEGF/MET inhibitor that recently demonstrated PFS and OS advantage over everolimus [17].

Checkpoint inhibitors and immunomodulators in the treatment of RCC

A new area of investigation in cancer chemotherapy involves the specific targeting of regulatory pathways of the immune response. The advent of checkpoint inhibitors has revolutionized systemic therapy for RCC where multiple PD-1, PDL-1 and CTLA-4 inhibitors have demonstrated responses and improved survival but only in minority of individuals after managing the toxicities. Combination immunotherapy is an active area of research where researchers wish to know the mechanism of response and resistance and finally managing the autoimmune toxicities.

T-cells recognize antigens associated with MHC as the first signal but additional signals via co receptors are required for optimal T-cell recognition and generation of potent and long -lasting T-cell immune response These additional signals involve agonist co-receptors such as CD4 and inhibitory co-receptors such as cytotoxic T lymphocyte antigen (CTLA-4) and programmed death (PD-1). Antibodies to these T cell immunomodulatory co receptors have been developed which when bind to the antigens either accentuate or attenuate the T cell response [12].

Cabozantinib

The second-line agents everolimus and axitinib had become the standard of care after the failure of 1st line therapy but studies found that the mPFS was only extended by a mere 3 to 5 months after disease progression on first-line therapy. Cabozantinib and lenvatinib being the novel drugs have gained FDA approval for use in advanced RCC [12].

PD-1 blockade

PD-1 is a transmembrane protein expressed on the activated T cells. It has two known ligands, PD-L1 and PD-L2 which can be expressed on a variety of cells including antigen presenting cells, tumor cells and T cells themselves. When bound to its ligands PD-1 being the inhibitory co-receptor inhibits the signaling pathways that lead to an effective T-cell response. PD-1 limits the activity of T-cells in the periphery of the primary lymphoid organs during the inflammatory response [13].

- **Nivolumab**

Recently approved by USFDA as a second line therapy followed by antiangiogenic failure in patients with advanced RCC. The drug was also compared with everolimus and the objective response rate was found to be higher with nivolumab than everolimus. Combination with bevacizumab is also being explored in presurgical setting [12, 18].

- **Pembrolizumab**

It is a humanized IgG4 PD-1 blocking antibody and is being studied as monotherapy and in combination with lenvatinib, axitinib and pazapanib. Studies show that the combination is well tolerated and exhibits anti-tumor activity in treatment -naïve patients.

PD-L1 inhibitors

Durvalumab-currently being studied as a immunotherapy and in combination with CTLA-4 inhibitor tremelimumab.

Atezolizumab-USFDA approved currently being evaluated in combination with bevacizumab.

Avelumab-An ongoing study of avelumab with axitinib showed tolerability, safety and significant anti-tumor activity in treatment naïve patients [12, 19].

CTLA-4 blockade

Another novel checkpoint that is expressed on activated T cells and has been targeted successfully is CTLA-4. Its induces inhibitory signaling which leads to decreased T cell proliferation. CTLA4 blockade is established by ipilimumab and tremelimumab which were evaluated with

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sunitinib but the risk of renal toxicity outweighed the benefit due to which the study was abandoned [12].

Vaccine Therapy

Vaccine therapy has shown promising results mainly in the adjuvant setting after nephrectomy in higher risk patients to prevent disease relapse. Immune-stimulating approaches have shown low but reproducible response rates in patients. Approaches have included gene-modified tumor cells and dendritic cell–based vaccines. Reniale, a patient-specific vaccine using lists from autologous tumors cells extracted at the time of surgery showed promising results but study design which should be appointed during the clinical trials posed another challenge. Some vaccines (e.g., Oncophage) resulted in controlling patients with only small-volume disease. Other vaccines (like Trovax) use single-cancer antigens that may cause treatment escape through down regulation or total expression loss. It can be concluded that since vaccine clinical trials require highly optimized conditions, the development program should not be based on just immune response but on clinical data. Some rare vaccines that generate very little B-cell or T-cell responses do not induce sufficient effector function to cure tumors or to overcome immunosuppression caused by the malignancy [20].

Novel checkpoints

Thalidomide-It is a potent immunomodulatory drug with anti-angiogenic properties and has been shown to have potential activity in RCC. Lenalidomide is a thalidomide derivative with the same properties. In a study low dose thalidomide resulted in manageable toxicity, better response rates, progression free survival and overall survival in the study population [21, 22].

Personalized Therapy

The priority for research should be to determine how to select the best therapy for the patient because already the patient is mentally diseased to be a victim of cancer and switching drug classes makes it very difficult for the patient to cope up. So it is of utmost importance to know how to use the drugs available in the market. If one drug works for 30% of patients, we need to identify 30% that should be given the drug The effort of personalized therapy is that treatments can be aimed at a pathway specific to the individual's cancer — selecting the right drug for the right patient. Instead of flooding RCC with drugs that target several pathways, the target should be determined first like treating only those patients with m TOR inhibitors who have m TOR aberration in the pathway. In order to personalize the therapy, doctors need to test the most relevant pathway responsible for the development of the disease. This includes biomarkers or genomic and next-generation sequencing methods to determine the phenotype of the tumor. So the selection of the therapy should be done after examining the phenotype of the tumor. Personalizing therapy would not only be more efficient, but would also help to prevent the accumulated adverse impacts of taking several drugs at once. Researchers also need to understand how long drugs need to be given and their respective doses [23].

CONCLUSION

The treatment of advanced renal cell cancers has evolved significantly with the application of new targeted agents such as bevacizumab, sunitinib, sorafenib, temsirolimus, and everolimus. Immunogenicity of RCC has provided unique treatment modalities in the past, comprizing high-dose IL-2 and interferon, which remained the mainstay of systemic management for patients with metastatic RCC for several decades. The recent past has seen reduced use of interferon after the introduction of targeted agents, which have shown progression-free survival benefit compared with interferon in large clinical trial settings. The challenge will be how to sequence or combine these new agents for optimal results. Better understanding of renal biology has resulted in the development of novel hormonal drugs and a variety of cytotoxic and targeted agents.

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