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Review Article

Immunotherapy in Metastatic Renal Cell Carcinoma

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Abstract

Immunotherapy plays a crucial role in the treatment of patients with renal cell carcinoma. Metastatic renal cell carcinoma (MRCC) remains a therapeutic challenge because of its strong resistance to both chemotherapy and radiation therapy. This review explains the advancements of new biologics for the treatment of metastasized renal cell carcinoma with the use of cytokines, interleukin – 2 (IL-2), lymphocyte killer cells (LKC), and IFN alpha. Several immunotherapeutic approaches are being in use for the management of the MRCC, which includes inactivated tumor cells and genetically modified tumor vaccines (GMTV), peptide-based vaccines, and dendritic cells. The role of CD4+ T cell and CD8+ immunity in tumor protection in animal models is also discussed.

Keywords: Immunotherapy; Metastatic Renal Cell Carcinoma (MRCC); Vaccines; Chemotherapy; Cytokines; CD4+ T Cell and CD8+ Immunity; Tumor Protection; IFN Alpha; Peptide-Based Vaccines and Dendritic Cells.

Introduction

Renal cell carcinoma (RCC) is the most common type of kidney cancer in adults that originates in the lining of proximal convoluted tubule (PCT) in the kidney [1]. The tubule is lined by simple cuboidal epithelium and with brushed borders, which help to increase the maximum area of absorption. It is known as one of the fatal genitourinary tract cancer with 40 % of death rate [2]. Renal cell carcinoma becomes metastatic renal cell carcinoma (MRCC) when the disease tumors starts spreading from the kidney to the other neighboring body parts such as lymphatic system, as well as distant involvement of the lungs, bones, or other organs [3]. Daniel Sennert mentioned tumor in kidney in his text "Practicae Medicinae" first time in 1613 [4].

Epidemiology

American Cancer Society estimated around 63,920 new cases of renal cancer (39,140 in men and 24,780 in women) and about 13,860 deaths (8,900 men and 4,960 women) due to renal cell carcinoma in the U.S. in 2014 [5].The ratio of incidence and prevalence in males and females is around 1.5:1 and renal cancer is one of the common causes of death at an average age of 45 in both sexes [6].

The RCC does not have any specific symptom at the initial stage, until the tumor has grown larger. The triad for diag-

nosis of the RCC is hematuria, flank pain [7] and palpable mass [8] that is clinically detectable in about 10% of patients. Fever of unknown origin (FUO) [9] and other clinical presentations such as polycythemia, hypertension and tumor thrombosis with extension to inferior vena cava and even right atrium are not uncommon. Sudden, painful unilateral (mostly left side) varicocele may also an indication of RCC in left kidney. It is also known as "Internist;s Tumor" because of its multiple signs and symptoms.

Classification of Renal cell carcinoma:

WHO introduced a broad classification of renal cell carcinoma in 2004 which is based on pathology and genetic abnormalities [10].

Diagnosis for Renal Cell Carcinoma:

After considering the signs and symptoms, physical examinations can direct for further investigations. Laboratory tests includes serum creatinine, serum corrected calcium, leukocyte counts, hemoglobin, platelet counts, lactate dehydrogenase, C-reactive protein (CRP: a pentameric protein present in the blood plasma), and ESR (erythrocyte sedimentation rate). Clinical symptoms or painless hematuria should be followed carefully with imaging studies (such as Ultrasound and CT scan with intravenous contrast media or MRI as a diagnostic modality) followed by tissue diagnosis and staging. Histopathological diagnosis includes biopsy that is required to be done prior to start of treatment [11].

Familial Renal cell carcinoma	
Renal cell tumor	**Malignant**
	· Clear cell Renal cell carcinoma
	· Multilocular clear cell renal cell carcinoma
	· Papillary renal cell carcinoma
	· Chromophobe renal cell carcinoma
	· Carcinoma of the collecting ducts of Bellini
	· Renal medulary carcinoma
	· Xp11 translocation carcinomas
	· Carcinoma associated with neuroblastoma
	· Mucinous tubular and spindle cell carcinoma
	· Renal cell carcinoma unclassified
	Benign
	· Papillary adenoma
	· Oncocytoma
Metanephric Tumor	· Metanephric adenoma
	· Metanephric adenofibroma
	· Metanephric stromal tumors
Mixed mesenchymal and epithelial tumors	· Cystic nephroma
	· Mixed epithelial and stromal tumor
	· Synovial sarcoma
Nephroblastic tumors	· Nephrogenic rests
	· Nephroblastoma
	· Cystic partially differentiated nephroblastoma
	· Neuroendocrine tumors
	· Carcinoid
Neuroendocrine carcinoma	· Primitive neuroectodermal tumor
	· Phaeochromocytom
Other tumors	· Mesenchymal tumors
	· Hematopoietic and lymphoid tumors
	· Germ cell tumors
	· Metastatic tumors

Table 1. WHO classification of RCC based on pathological and genetically abnormality.

The treatment of metastatic renal cell carcinoma (MRCC) is challenging, because of its ineffective results with chemotherapy and radiotherapy [12]. Primary method of treatment is still surgery, which remains the backbone of curative treatment. Three kinds of major surgeries are performed in patients with renal cell carcinoma.

Radical nephrectomy (removal of kidney, adrenal gland, perirenal fat, and gerota fascia): for localized RCC.

Nephron-sparing surgery (partial nephrectomy): This is successful in normal contralateral kidney if the tumor is <4 to 7 cm. This can be performed through laparoscopic or coelioscopic robot assisted technique. For tumor with size greater than 7 cm, laparoscopic radical nephrectomy is preferred.

Bilateral radical nephrectomy: in cases if both the kidneys are affected.

Targeted Therapies for MRCC

Bevacizumab: Bevacizumab is a first humanized angiogenesis inhibitor monoclonal antibody which is approved by FDA. It is used for the treatment of renal cell carcinoma and it binds to the vascular endothelial growth factor (VEGF) protein which neutralizes the blood vessel circulation. In a phase III of CALGB 9020 clinical trial, the combination of bevacizumab (Avastin) and interferon- α indicated important results rather than INF-α as a monotherapy.

Everolimus: According to FDA, everolimus is an immunosuppressant, indicated for the treatment of advanced renal cell carcinoma. It inhibits a type of protein called mammalian target of rapamycin (mTOR), which is responsible for angiogenesis and tumor cell division. In 2008, Robert J Motzer and other have done a randomized, placebo controlled, and double blind phase III of clinical trials to determine the efficacy of everolimus in mRCC patients because these patients already have been suffered from the progression of this disease after the treatment with VEGF therapy. In this trial, 272 patients were administered with 19mg everolimus daily and 138 patients with placebo. The registration number of this experiment is NCT00410124. These all patients were subjected to the efficacy analyses and various clinical results were analyzed in a positive response manner. There was total 191 different progression events occurred in which 101 events in everolimus group and 90 in the placebo group. The clinical result of the treatment with everolimus was the continuation of PFS in comparison with placebo group which occurred after the treatment with different therapies [13].

Sunitinib Malate: Sunitinib is a malate multi-kinase inhibitor which is approved by FDA in 2006 with a brand name "Sutent" for the treatment of MRCC [14]. In a study, 750 patients were registered and these were earlier untreated. The metastatic renal-cell carcinoma received continuous six week cycles of sunitinib (4 weeks with single dose of 50 mg and 2 weeks without treatment) or interferon- α (9 MU dose given three times weekly) in a randomized, multicenter, phase 3 of clinical trial.

Column1	Column2	Column3	Column4	Column5	*Column6*
Endpoint		Avastin + IFN	Placebo + IFN	HR(Hazard ratio) (95% CI (confidence interval))	*P* value
					(probability of obtaining a result)
	Number of patients	327	322		
Primary	PFS (median)	10.2 months	5.4 months	0.60(0.49–0.72)	<0.0001
Initial primary*	OS (median)	23 months	21 months	0.86 (0.72–1.04)	0.1291
Secondary	ORR (overall response rate)	30% (n=306)	12% (n=289)		<0.0001

Table 2. PFS and OS data of Avastin [Avastin Prescribing Information. Genentech, Inc. August 2014, Data on file [11].

In this experiment, the progression free survival was the primary end point and the secondary end points involved in the safety, patient-reported outcomes, overall survival, and objective response rate. The average time of progression free survival for sunitinib group was 11 months as comparison to the interferon- α group which was having 5 months, equivalent to a threat ratio of 0.42. Sunitininb was having higher objective response rate 31% a compare to interferon- α, which was having only 6%. The MRCC patients were having higher response rates and progression free survival who received sunitinib rather than interferon- α [15].

Sorafenib: Escudier B et al conducted a phase III trial in 2012 in which PFS was 5.5 months in the sorafenib group whereas 2.8 in placebo group. Overall survey done in 2005 and its clinical outcome showed reduced rate of death, but it had some adverse event such as diarrhea, hand-foot skin, fatigue and rashes [11].

Pazopanib Hydrochloride: Pazopanib hydrochloride is an oral multi-targeted tyrosine kinase inhibitor and it is having anti-tumor activity. It inhibits c-kit, platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR) -1, -2 and -3 signaling pathway and it may result in the inhibition of angiogenesis in different tumors in which these receptor are free. The outcomes of Pazopanib are overall survival, response rate, health related quality of life, progression free survival, and adverse effects of treatment [16]. It is a current drug which is presented in the oncology medicine collection for the treatment of predominantly clear-cell RCC patients and its toxicity profile is comparable to the other anti-angiogenic drugs which are used in the treatment of renal cell carcinoma. The side effects data for this treatment are still awaited [17].

Aldesleukin: Aldesleukin is a subtype of cytokines which enhance the metabolism process of body to compete the cancer. FDA approved this aldesleukin as the name of Proleukin and it involves in increasing the immunoregulatory properties, which includes activation of natural killer cell, lymphocytes cytotoxicity, and the production of interferon- γ [18, 19].

Temsirolimus: Temsirolimus is a mammalian target of rapamycin (mTOR) inhibitor and it is used intravenously for the treatment of RCC. Temsirolimus is a FDA approved drug and its mechanism of action involves in the inhibition of mTOR. Temsirolimus binds to intracellular binding protein (FKBP-12), and resultant protein-drug complex forms, which inhibits mTOR kinase activity. Their activities control the cell division which results the disturbance occurs in the G1 –phase of tumor cell. When mTOR get inhibited then it blocks the PI3 kinase and AKT pathway that helps in the phosphorylation of p70, S6 kinase and also ribosomal protein S6. In-vitro, renal cell lines were finished and resulted in the HIF-1 α and HIF-2 α and vascular endothelial growth factor (VEGF) levels. Treatment options have been changed from IL-2 (16.3%) and IFN alpha (16.6%) to Temsirolimus (15.2%) in 2009.

Contemporary approach of targeted therapy for RCC:

The inactivated von Hippel Lindau (VHL) gene characterized as a most common clear cell type of RCC [20]. Von Hippel Lindau (VHL) hypoxia inducible factor played a vital role in the biological process of Clear cell type RCC. There are two main methodologies for targeting the cancer and that are the blockage of VEGF pathway and mTOR pathway [21]. First is the angiogenesis inhibitor, e.g. bevacizumab with IFN- α combination which targets VEGF pathway and second is the inhibition of mammalian target of rapamycin (mTOR) signaling due to the treatment with everolimus and temsirolimusa [22].

Immunotherapy in metastatic renal cell carcinoma (MRCC):

Non-surgical treatment for RCC showed very limited significant clinical outcome in the past due to its resistance to chemotherapy [23]. In recent years, due to advancement of immunotherapy, it helps by interfering the cancer cell growth at a molecular level with natural defence mechanism.

Cytokines are the main drugs which are used for the treatment of kidney cancer. MRCC patients treated with cytokines such as interleukin (IL)-2 and IFN-α which indicates the potential role of immunotherapy in the renal cancer.

T-cell based immunotherapy using natural or gene-modified T-cells have shown success in treating patients with metastatic RCC. Cytokines were considered as the standard of care before the initiation of new targeted agents such as, tyrosine kinase inhibitors (TKI) (sorafenib and sunitinib, axitinib and pazopanib), mTOR inhibitor (temsirolimus), and monoclonal antibody against vascular endothelial growth factor (bevacizumab). It is fascinating that the high dose of interleukin-2 can produce a complete reduction in small numbers of patients. This is at the expense of considerable toxicity and thus careful patient selection by appropriate clinical and other criteria is required. In recent time, tumor immunotherapy using dendritic cell has been ushered to possess healing potential for malignant tumor [24]. Cytokine treatment is also known as non-specific immunotherapy, as it induces nonspecific anti-tumor activity [25].

Cytokines, such as tumor necrosis factor (TNF) alpha, interferon (IFN) alpha, IFN-beta, interleukin-4 (IL-4), and IL-6, interact directly with tumor cells, inducing the cells to either commit suicide or stop further growth. Several randomized clinical trials have been conducted to demonstrate cytokine therapy for patients with MRCC and suggests that two cytokines, interferon-alpha (IFN-α) and interleukin-2 (IL-2) produce tumor de-

terioration in 10% to 15% of patients with metastatic disease. However, the combinations of IL-2 and IFN-alpha showed improved response rates, with no effect on overall survival. The addition of other cytokines or chemotherapy to this combination has been investigated, but it was demonstrated that no desirable effects have been observed. Asymptomatic patients with limited pulmonary or soft-tissue disease are in advantage [26]. In 1984, LAK (lymphokine-activated killer) cell is reported for the treatment of tumor by inducible cultured cell [27].

There are two common non-specific immunotherapy options that are discussed below:

Interferon: Interferon enhances the immune system to fight against cancer and may reduce the growth of cancerous cell by regulation of gene functions. They are part of the natural defense system that is produced by adjacent normal cells in response to viral infections and cancer. Generally, three different subtypes of interferon are produced in the body: alpha, beta and gamma. The first two types are produced in response of both viral infections, and cancers and interferon gamma is mostly associated with cancer. Interferon alpha in both forms of alpha 2-aand 2-b are commercially available in different brand names such as (Roferon-A [2a], Intron A [2b], Alferon [2a]). These are the most common types of interferon used in the treatment of cancers. Side effects of administrating interferon include flu-like symptoms, rashes, an increased risk of infection and thinning hair. IFN-α is responsible for inducing Th-1 cytokine production, so it promotes anti-tumor activity of cells that elicits cytotoxicity by acting directly on the tumor. Recent research shows that IFN-γ in combination with tumor necrosis factor (TNF) has direct cytotoxic effects on tumor cells. Increased secretion of IFN-γ leads to increased MHC expression and may result in increased presentation to T cells.

Qin and Blankenstein have conducted several experiments which suggest that IFN γ production is important for non-hematopoietic cells to produce CD4+ T cell-mediated antitumor immunity. It has also been evidenced that IFN-γ has the ability to inhibit tumor induced angiogenesis and could prevent tumor growth through this mechanism [28].

According to a study, there were 463 patients with progressive renal cell carcinoma and interferon- α administered as the primary therapy on six different potential clinical trials which were focus on this retrospective analysis. There were three risk groups for forecast survival which were recognized on the basis of five different pretreatment clinical appearances through layered Cox proportional hazards model. The average of total survival time was 13 months and to evolution was 4.7 months. There were five variables of risk factor which was used for short survival: low Karnofsky performance status, high corrected serum calcium, low serum hemoglobin, high lactate dehydrogenase, and time from the diagnosis of initial renal cell carcinoma to start interferon- α therapy within one year. These risk groups were assigned to each patient: patient with zero risk factors (favorable risk) and its average time to death was 30 months, patient with one or two risk factor (intermediate risk) and its average time to death was 14 months, and patient with three or more than three risk factors (Poor risk) and its average time to death was 5 months. The interferon- α treatment with an average time of survival and free of evolution which can be compared with other new therapies in the investigation of phase II and phase III. The prognostic model is appropriate for different risk stratification of phase III clinical trials via interferon- α as the comparative treatment arm [29].

Interleukin: Interleukins also helps in the body's defense system, which produce cells that destroy cancer. In vitro,Interleukin-2 or aldesleukin (Proleukin) is used for the treatment of kidney cancer, skin cancer, including melanoma. Side effects of Interleukin-2 treatment are low blood pressure and weight gain, which can be cured with other combination of medications. Some person may also have flu-like symptoms [26].

A study stated that progressive renal cell carcinoma (RCC) is a chemoresistant disease. The response rate of immunotherapy with interleukin (IL)-2 is about 15%, but improved treatments are required. Interleukin (IL)-4 is a cytokine which is produced by activated CD4+ lymphocytes. Interleukin (IL)-4 has pluripotent activity and inhibits in-vitro proliferation of RCC cell lines. In this trial, patients were compulsory to have a diagnosis of renal cell adenocarcinoma by significant disease and status of performance (SWOG) of 0-1. The patients had to have satisfactory hepatic, bone marrow, and renal function and further no clinically important cardiac or pulmonary dysfunction. Interleukin (IL)-4 was administered through subcutaneous route at a dose of 5 micorg/kg/d, continuously for 28 days and followed by a rest period of 7 days. 58 patients were registered including 7 patients unqualified and 2 patients were not analyzable since these patients didn't get the treatment. Around 49 patients were identified as qualified and analyzable patients and there were no established partial or complete responses. There was only one unconfirmed partial response in the retro-caval lymph nodes but no verifying dimension was done. There were 16 patients whose valuation was insufficient to regulate the response, 25 patients with growing disease or progression, and 7 patients with steady state disease with no response. The average time to progression was 3 months and average survival time was 13 months. The toxicity was important with simple side effects such as headache or pain, diarrhea, malaise or fatigue or lethargy, vomiting, and nausea. There were 13 examples of grades four toxicity which happened in 9 patients and 3 patients had exceptional toxicities which comprised Bell's palsy hypoglycemia in an earlier well controlled diabetic. Despite auspicious immunologic and growth inhibitory effects, Interleukin (IL)-4 with this dose than it is not valu-

able for the treatment of RCC patients [30].

Advancements in Immunotherapy as a treatment alternative for MRCC:

Various immunologic-agent based studies have proven to be successful in the treatment of MRCC and hence, can provide advancement in the treatment options available at present. The advanced approach might include modalities like cytokine, dendritic cells, and vaccine-based immunotherapy. These approaches have been discussed below:

Prognostic factor CD 8(+) T-Lymphocytes and its role in renal cell carcinoma:

CD8(+) tumor-infiltrating cytotoxic T-lymphocytes (TILs) cells could be an expression of anti-tumor activity. Nakano and others in 2001 conducted a clinical trial and in this clinical trial, there were 221 patients with RCC without preoperative treatments. The sufficient infiltration or penetration of tumor tissue through CD8(+) as well as through CD4(+) T-cells, which was related with the shorter survival of the patients and this is because of a positive relationship between tumor grade factors and the number of lymphocytes. This proposes that the immune cell reactions are clear cut as the progresses of biological malignancy and tumor growth factor. The proliferative activity of CD8(+) T cells was analyzed that penetrated in the tumor cell shells, and it can reflect the anti-tumor immunity. Uni- and multivariate analyses for longer survival associated with Ki-67: a proliferation-associated antigen and it is among CD8(+) T cells in contact to tumor cells. Statically data suggest that the penetration of tumor tissue through T-cells than it doesn't show the effectiveness of anti-tumor immunity. This concept would be a major issue for the immunotherapy of RCC [31].

Genetically - modified autologous tumor-cell B7-1 vaccines for renal-cell carcinoma:

In the last decade, there are some extreme changes in the RCC treatment by the use of various immunologic approaches. The immune-modulatory cytokine interleukin-2 has been permitted for the treatment of RCC. The efficacy of immune-modulatory cytokine interleukin-2 is low but there is no other conventional method for treatment of mRCC patients. So, there is a requirement of the development of a novel treatment approach. Because of this reason, genetically modified autologous tumor cell vaccines were developed. There is a B7-1 vaccine which provides stimulation to tumor reactive cells. The reason of this approach is that T-cells require two different signals: binding of T cell receptor with major histocompatibility complex (MHC) and; CD-28 with B7-1. Meanwhile, B7-1 gene is not usually expressed by renal cell carcinoma due to the transfection effect of this gene which could make the tumor cells more immunogenic.

An experiment has been done in case of mice, in which tumor cell transfected with B7-1 and result was found that T cell mediated rejection of tumor cells. One of these methods has been applied for the treatment of mRCC patients. For phase-1, patients was enrolled and treated with autologous tumor cells which were modified to express B7-1 and it works as tumor vaccines. The metastases and other crucial tumors are resected from the patients and adapted to in-vitro culture and infected with a recombinant adenoviral vector which is containing human B7-1 cDNA and it is determined by the cytomegalovirus (CMV) promoter, and stored in liquid nitrogen. Vaccines of B7-1 gene-modified tumor cells are administered to the patients at different interval. The patients are also treated with systemic IL-2 along with increased tumor-reactive T-cells which is activated by the vaccine for this disease. The clinical response, immunogenicity, and toxicity of the vaccine are being evaluated at each of three dose levels in three to five patients [32].

Role of Dendritic cells (DCs) as an antigen specific vaccination in patients with MCC:

Antigen-specific vaccination with dendritic cells (DCs) has been shown to induce the response of cytotoxic T-cells in metastatic RCC patients. Therefore, different clinical trials using dendritic cells for immunotherapy of RCC treatment which is appear to be most promising. **Peter Middel and other** categorized the delivery of different mature and immature dendritic cells subsets in renal cell carcinoma tumor tissue and normal kidney tissue. In other analysis, the expression of several chemokine and its receptor controls the migration of dendritic cells subsets. It was found that the maximum number of immature CD1a+ DCs presented within the RCC tumor tissue. In a comparison with immature CD1a+ DCs, the aggregation of mature CD83+/DC-LAMP+ DCs were limited to the invasive margin of RCC tumor tissue. These mature DCs were responsible to form cluster with proliferative T cells and a close relationship was detected between MIP-3α-producing tumor cells and immature CCR6+ DC. Oppositely, SLC and MIP-3β expression was only spotted at the border of tumor, where CCR7 expressing mature DCs cells and T-cells formed clusters [33].

D.J. Schendel in 2007 stated that DC vaccine is safe for RCC patients but with minimal clinical efficacy. Mature DC particularly plays an important role in regulation of T cells [34].

In a clinical trial, 18 patients of RCC were analyzed in which T regulatory cells phenotypes was examined after using flow cytometry method. Higher number of T regulatory cells in peripheral blood lymphocyte compared. Significant increases in T regulatory cells have been seen in MRCC patients after two time immunotherapy [35].

Non-myeloablative Stem Cell Transplantation (NST) in treatment of renal cell carcinoma:

In recent years, the great achievement has been done in field of molecular biology such as transplantation of hematopoietic stem cell. The donor mediated graft vs. tumor effect is most effectively and widely used in cancer immunotherapy [36].

NST was performed by Childs in 2000 on 19 renal carcinoma patients and achieved a success rate of 53%, among which three patients were in complete remission and seven patients were in partial remission. Cellular anti-tumor immunity mediates donor T cells in graft versus host disease (GVHD) and the graft versus tumor effect (GVT) and the appearance of GVHD induced by transplantation of donor T cells is inversely correlated with the rate of tumor recurrence. T cell-depleted stem cell transplants showed high recurrence and the administration of donor lymphocytes which reduces the incidence of recurrence [37-38].

Regulatory role of CD4+ T Cells:

The various roles of CD4 T cell immunity in tumor protection in animal models and putative mode of action, tumor antigens recognized by human CD4 T cells, and the cooperation between two CD4 T cells of different specificity as a response against sub-immunogenic determinants of tumor antigens in a tolerant environment, and the negative impact of regulatory CD4 T cells on anti-tumor T cell responses [39].

A study shows that increased numbers of CD4+, CD25+ T regs can be found in patients with advanced cancer [40] and that high T reg frequency are associated with reduced survival. CD4+ T cells play a crucial role in the control of tumor immune response and protecting the host against the development of autoimmunity by regulating immune responses against antigens expressed by normal tissues [41-42]. CD4+ T cells constitutively expressing the IL-2 receptor α-chain (CD25) and act in a regulatory capacity by suppressing the activation and function of other T cells [43].

Dannull et al used a recombinant IL-2: diphtheria toxin conjugate (DAB389IL-2; also known as Denileukin Diftitox) to eliminate CD25-expressing T regs in metastatic RCC patients, and reported that depletion of T regs in RCC patients followed by vaccination with tumor RNA-transfected dendritic cells lead to improve stimulation of tumor-specific T cells compared with vaccination alone [44].

The thymus derived naturally occurring FOXP3+, CD4+, CD25 high T regs have been shown to suppress the proliferation, activation and effector function of both innate and adaptive lymphocytes as well as APCs. Several studies have demonstrated that the number of CD4+ and FoxP3+Treg cells was significantly decreased after IFN-α treatment in patients receiving cytokine therapy, and T reg cell levels before treatment correlated with the clinical response [8]. The significant role of CD4+CD25+ T regs to control tumor growth which was further pointed by the revelation that depletion of T regs using anti-CD25 antibodies evokes effective antitumor immunity in mice [45,46].

Effect of CD8+ T cells in antitumor immunity:

T cell immunity is the important key to protect immune responses against tumors. Usually, this function has been attributed to CD8+ T lymphocytes with cytotoxic activity, which is controlled by MHC class I. CD8+ T cells can also be helpful in inducing antitumor immunity like CD4+ T cells. CD4+ T cells are recognized by only antigens presented by MHC class II, and secondly, CD8+ T cells, upon being presented with antigen by MHC class I, can directly destroy the tumor cell, through mechanisms.

McGray et al investigated the mechanisms of vaccination in 2014, which restricts the regression of the tumor activity by using a murine melanoma model. Adaptation capability of the tumor is very rapid to know that the immune attack starts by CD8+ T cell after following the vaccination, which results in the various types of immunosuppressive process. As a result, this local immune attack gets inhibited due to rapid adaption capability of the tumor cells. Combination vaccination along with tumor specific T cells induces the activity of the regression of the tumor, which have been treated but unable to prevent the emancipation. A mice with tumor, was immunized with recombinant adenovirus vaccines expressed dopachrome tautomerase or gp100, yielded in response of antigen specific CD 8+ T cell. Tumor growth was slowing reported in the dopachrome tautomerase and unaffected in other mouse which has been given gp100. Growth inhibition of the tumor cells was mediated by CD 8+ T cells [47].

Conclusions

Immunotherapy is as an effective therapy against in the management of patients with metastatic renal cell carcinoma (MRCC). The immunotherapy using cultured cells, such as DCs and humanized antibodies, which are used for the treatment of patients with MRCC and conduction of a number of scientific experiments due to a number of problems associated with the requirement of adequate culture facilities and appropriate culture techniques. It was also demonstrated that earlier the use of DCs was highly appreciated, but nowadays, interleukins and interferon are being in use. Because of high resistance to both conventional chemotherapy and radiation therapy, there is a progressive need for the analysis of the mechanisms involved in tumor immunity and the development of new immune-based therapies. It was observed that the use of monoclonal antibodies and tumor vaccines shows moderate response for patients with MRCC, whereas treatment with cytokines including IL-2, and IFN alpha shows positive response

in patients. Several immunotherapeutic approaches are being in use for the management of the RCC, which includes inactivated tumor cells and gene modified tumor vaccines (GMTV), peptide-based vaccines, and other CD4+ T cell and CD8+.

Abbreviations

Renal cell carcinoma (RCC), interferon alfa (IFN-α), antigen-presenting cells (APC), regulatory T cells (Treg cells), dendritic cell- (DC-), tumor necrosis factor (TNF), Food and Drug Administration (FDA), lymphokine-activated killer cells (LAK), tumor-infiltrating lymphocytes (TIL), genetically modified T cells (GMTC), interferon (IFN), major histocompatibility complex (MHC), Human papillomavirus *(HPV),* cytolytic T cells (CTLs), autologous tumorlysate (TuLy), Non-myeloablative Stem Cell Transplantation (NST), graft versus host disease (GVHD), graft versus tumor effect (GVT),inducible nitric oxide synthase (INOS), galactosylceramide (GalCer), FOXP3(fork head box P3), diphtheria toxin conjugate (DAB389IL-2) and nitric oxide (NO).

References

1. Curti B, Jana BRP, Javeed M, Makhoul I, Sachdeva K et al. Renal Cell Carcinoma. JE WebMD. 2014.
2. yashree R. RCDB: Renal Cancer Gene Database. BMC Research Notes. 2012, 5(246).
3. Master VA. Renal Cell Carcinoma', Merck Manual Professional. Merck Sharp & Dohme Corp. 2013.
4. Delahunt B. History of Renal Neoplasia. United States and Canadian Academy of Pathology 2009 Annual Meeting. 2009.
5. Lane BR. Prognostic Factors for Localized Renal Cell Carcinoma. Current Clinical Urology. 2013, 83–102.
6. American Cancer Society: Cancer Facts and Figures 2014. Atlanta: American Cancer Society. 2014. Available online. Last accessed on 2014.
7. Cohen HT, McGovern and Francis J. Renal-Cell Carcinoma. New England Journal of Medicine. 2005, 353(23): 2477–2490.
8. Motzer RJ, Bander NH and Nanus DM. Renal-Cell Carcinoma. New England Journal of Medicine. 1996; 335(12): 865–875.
9. Kim HL, Belldegrun AS, Freitas DG, Bui MHT, Han KEN-RYU et al. Paraneoplastic Signs and Symptoms of Renal Cell Carcinoma: Implications for Prognosis. The Journal of Urology. 2003, 170(5): 1742–1746.
10. Lopez-Beltran A, Scarpelli M, Montrioni R and Kirkali Z. WHO classification of the Renal Tumors of the adults. European Urology. 2006, 49: 798-805.
11. Escudier B, Eisen T, Porta C, Patard JJ, Khoo V et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2012; 25(3): iii49-iii56.
12. Delahunt B. History of Renal Neoplasia. United States and Canadian Academy of Pathology 2009 Annual Meeting. 2009.
13. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. The Lancet. 2008, 372(9637): 449 – 456.
14. Pazdur R. FDA Approval for Sunitinib Malate. 2011.
15. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. New England Journal of Medicine. 2007, 356(2): 115-124.
16. Pazopanib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. National Institute for Health and Clinical Excellence. 2009.
17. Zivi A, Cerbone L, Recine F and Sternberg CN. Safety and tolerability of pazopanib in the treatment of renal cell carcinoma. Expert Opin Drug Saf. 2012, 11(5): 851-859.
18. Doyles MV, Lee MT, Fong S. Comparison of the biological activities of human recombinant interleukin-2125 and native interleukin-2. J Biol Response Mod. 1885, 4: 96109.
19. Ralph P, Nakoinz I, Doyle M. Human B and T lymphocyte stimulating properties of interleukin-2 (IL-2) muteins. In: Immune Regulation by Characterized Polypeptides. Alan R. Liss, Inc. 1887: 453-62.
20. Clifford SC, Prowse AH, Affara NA, Buys CH and Maher ER. Inactivation of the von Hippel-Lindau (VHL) tumour suppressor gene and allelic losses at chromosome arm 3p in primary renal cell carcinoma: evidence for a VHL-independent pathway in clear cell renal tumourigenesis. Genes Chromosomes Cancer. 1998, 22(3): 200-209.
21. Rini BI, Atkins MB. Resistance to targeted therapy in renal-cell carcinoma. Lancet Oncol. 2009, 10: 992–1000.
22. Mulders P. Vascular endothelial growth factor and mTOR pathways in renal cell carcinoma: differences and synergies of two targeted mechanisms. BJU Int. 2009, 104(11): 1585-1589.
23. Motzer RJ, Russo P. Systemic therapy for renal cell carcinoma. Journal of Urology. 2000, 163: 408–417.
24. Wierecky J, Mueller M, Brossart P. Dendritic cell-based cancer immunotherapy targeting MUC-1. Cancer Im-

munology. Immunotherapy. 2006, 55(1): 63–67.

25. Itsumi M, Tatsugami K. Immunotherapy for Renal Cell Carcinoma. Clinical and Developmental Immunology. 2010, 1-6.

26. Lee AW, Truong T, Bickham K, Fonteneau JF, Larsson M, Da Silva I et al. A clinical grade cocktail of cytokines and PGE2 results in uniform maturation of human monocyte-derived dendritic cells: implications for immunotherapy. Vaccine. 2002, 20(14): A8-A22.

27. Mule JJ, Shu S, Schwarz SL, Rosenberg SA. Adoptive immunotherapy of established pulmonary metastases with LAK cells and recombinant interleukin. Science. 1984, 225(4669): 1487–1489.

28. Qin Z, Blankenstein T. CD4+ T cell-mediated tumor rejection involves inhibition of angiogenesis that is dependent on IFNγ receptor expression on nonhematopoietic cells. Immunity. 2000, 12(6): 677–686.

29. Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol. 2002, 20(1): 289-296.

30. Whitehead RP, Lew D, Flanigan RC, Weiss GR, Roy V et al. Phase II trial of recombinant human interleukin-4 in patients with advanced renal cell carcinoma: a southwest oncology group stud. J Immunother. 2002, 4: 352-358.

31. Nakano O, Sato M, Naito Y, Suzuki K, Orikasa S et al. Proliferative activity of intratumoral CD8(+) T-lymphocytes as a prognostic factor in human renal cell carcinoma: clinicopathologic demonstration of antitumor immunity. Cancer Res. 2001, 61(13): 5132-5136.

32. Antonia SJ, Seigne JD. B7-1 gene-modified autologous tumor-cell vaccines for renal-cell carcinoma. World J Urol. 2000, 18(2): 157-163.

33. Middel P, Brauneck S, Meyer W, Radzun HJ. Chemokine-mediated distribution of dendritic cell subsets in renal cell carcinoma. BMC Cancer. 2012, 10(578).

34. Chendel DJ. Dendritic cell vaccine strategies for renal cell carcinoma. Expert Opin Biol Ther. 2007, 7(2): 221-232.

35. Schwarzer A, Wolf B, Fisher JL, Schwaab T, Olek S et al. Regulatory T-Cells and Associated Pathways in Metastatic Renal Cell Carcinoma (mRCC) Patients Undergoing DC-Vaccination and Cytokine-Therapy. 2012.

36. Carvallo C, Childss R. Nonmyeloablative stem cell transplantation as immunotherapy for kidney cancer and other metastatic solid tumors. Cytotechnology. 2003, 41(2-3): 197–206.

37. Horowitz MM, Gale RP, Sondol PM. Graft versus leukemia reactions after bone marrow transplantation. Blood. 1990, 75(3): 555-562.

38. Kolb JH, Mittermuller J, Clemm C. Donor leukocytes transfusion for the treatment of recuurent chronic myleogenous leukemia in marrow transplant patients. Blood. 1990, 76(12): 2462-2465.

39. Kalams SA and Walker BD. The critical need for CD4 help in maintaining effective cytotoxic T lymphocyte Responses. J. Exp. Med. 1998, 188(12): 2199-2204.

40. Woo EY and Yeh H. Cutting edge: regulatory T cells from lung cancer patients directly inhibit autologous T cell proliferation. Journal of Immunology. 2002, 168(9): 4272–4276.

41. Jonuleit H, Schmitt E, Schuler G, Knop J, Enk AH. Induction of interleukin 10-producing, nonproliferating CD4 T cells with regulatory properties by repetitive stimulation with allogeneic immature human dendritic cells. Journal of Experimental Medicine. 2000, 192(9): 1213-1222.

42. Read S and Powrie F. CD4 regulatory T cells. Current Opinion in Immunology. 2001, 13(6): 644–649.

43. Shevach ES. Certified professionals: CD4CD25 suppressor T cells. Journal of Experimental Medicine. 2001, 193(11): F41–F45.

44. Dannull J, Su Z, Su Z. Enhancement of vaccine-mediated antitumor immunity in cancer patients after depletion of regulatory T cells. Journal of Clinical Investigation. 2005, 115(12): 3623–3633.

45. Shimizu J, Yamazaki S, Sakaguchi S. Induction of tumor Immunity by removing CD25+CD4+ T cells: a common basis between tumor immunity and autoimmunity. Journal of immunology. 1999, 163(10): 5211-5218.

46. Tatsugami K, Eto M, Harano M. Dendriatic cell therapy after nonmyloablative stem cell transplantation for renal cell carcinoma. Lancer Oncology. 2004, 5(12): 750-752.

47. McGray AJR, Hallett R, Bernard D, Swift SL, Zhu Z et al. Immunotherapy-induced CD8+ T Cells Instigate Immune Suppression in the Tumor. Molecular Therapy. 2014, 22(1): 206–218.