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Case Report
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Tislelizumab Combined with Arotinib in the Treatment of Advanced Renal Clear Cell Carcinoma: A Case Report and Review of Literature

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Abstract

Based upon MSKCC or IMDC, the Metastatic Renal Cancer (MRCC) prognosis model is considered to be low, intermediate, and high risk. Targeted therapy and immunotherapy play a major role in the first-line treatment of advanced renal cancer. Because of drug resistance and high treatment costs, it is necessary to explore new treatments to reduce the economic burden while prolonging the survival time of patients as long as possible.

The present case concerns a case of a 62-year-old man presenting with multiple metastases after radical left nephrectomy. The patient received first-line chemotherapy with vinorelbine combined with fluorouracil. After 4 cycles, Brain metastases decreased significantly. Nevertheless, disease progressed after 6 cycles. Tislelizumab and Anlotinib were prescribed. After 3 months, the brain metastases, both lungs and bilateral adrenal metastases reduced, and the bone metastases were stable, the condition remained stable after 15 months.

The study is the first to propose the effectiveness of vinorelbine combined with fluorouracil in treating MRCC, while proposing a new treatment model targeted in combination with PD-1, with fewer side effects and less cost. Owing to one patient was observed in this report, further exploration of the efficacy and safety of the combination regimen is needed later on.

Keywords: Metastatic renal cell carcinoma; Tislelizumab; Arotinib

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Introduction

Renal Cell Carcinoma (RCC) is the most common malignant tumor of the kidney, with increasing year by year [1]. About 400 thousand new RCC are reported on a world-wide scale, making up 5% and 3% in men and women, respectively [2]. The onset of RCC is insidious, and distant metastasis has taken place in about 30% of patients at the time of initial diagnosis, while about 30% still have recurrent metastatic after radical RCC [3]. Common metastatic sites of RCC are lung, bone, liver, adrenal gland and brain, while most patients with bone metastases can involve spinal [4,5]. MRCC has an extremely poor prognosis, with a 5-year survival rate of less than 10% and a median OS of less than 12 months [6]. Targeted therapy and immunotherapy represented by sunitinib and pembrolizumab are first-line drugs for MRCC and have improved the survival status of MRCC patients, but cost is extremely high [7]. Hence, we present a new treatment model in the form of case report and review the treatment progress of MRCC.

Case Presentation

A 74-year-old male with a left kidney occupation during physical examination on June 05th, 2016, underwent "posterior laparoscopic radical left nephrectomy" on June 12th, 2016. Postoperative pathology: (left kidney) clear cell carcinoma with necrosis, Furhman grade 2. The results of Immunohistochemistry (IHC) staining were positive for Cam5, CD10, EMA, and negative for CK7, CD117, HMWCK, CK20 and GATA3. The postoperative stage took place in stage pT3N0M0 III stage. On June 25th, 2020, the patient had a cough and headache. Computed Tomography (CT) showed that there were multiple metastasis in the bilateral cerebellar hemisphere with the larger diameter of about 1.1 cm, accompanied by the pons, bilateral frontal lobe, parietal lobe, temporal lobe, occipital lobe, right semioval center and right basal ganglia, with bilateral lung and bilateral

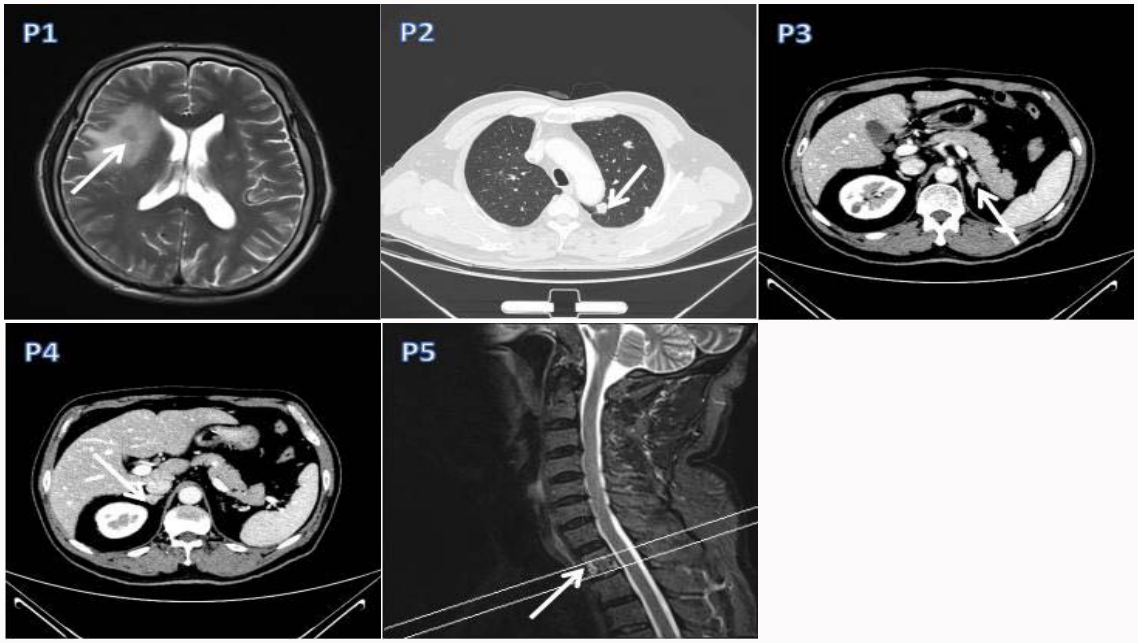

Figure 1: Size of tumor metastasis before treatment. P1 brain metastasis, P2 left lung metastasis; P3 left adrenal metastasis, P4 right adrenal metastasis, P5 thoracic 1 vertebral metastasis.

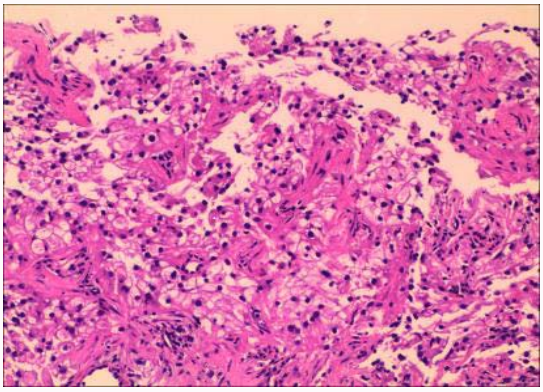

Figure 2: The histopathological examination of left lung space occupying puncture was consistent with that of metastatic renal clear cell carcinoma. The lesion showed a large number of clear tumor cells with small nucleus, rich cytoplasm and reticular fibrous vascular stroma around.

adrenal gland and thoracic 1 vertebral metastasis (Figure 1). Pathological examination results of the position-occupying puncture of the left lung: Metastatic Renal Clear Cell Carcinoma (CcRCC) (Figure 2). IMDC is score1, intermediate risk.

The patients was administered the first-line chemotherapy with Vinorelbine (45 mg day 1, day 8 intravenous drip, q3w) with fluorouracil (540 mg day 1-3 intravenous drip) from July 2020 to November 2020 for 6 cycles. Brain metastases decreased after 2 and 4 cycles, and efficacy was evaluated as stable (SD), However, the brain metastasis progressed after 6 cycles.

As second line therapy, Tislelizumab 200 mg Q3W and Anlotinib 12 mg/day were prescribed on January 14th, 2021. After 3 months, metastasis in the bilateral cerebellar hemisphere shrunk significantly and partially disappeared with the lager diameter 0.5 cm. Both lung and bilateral adrenal metastasis decreased, and thorough 1 metastasis was stable (Figure 3). The efficacy was evaluated after 6 months to maintain SD. The adverse reactions during the treatment were swollen and painful gums, diarrhea, which improved after symptomatic treatment. Until March 15th, 2022, the patient had obtained a 15-months Progress-Free Survival (PFS). The treatment process of the patient is shown in Table 1.

Table 1: Treatment detail of the MRCC patient.

Sex	Male
Age	62
Smoking history	No
family history	No
Surgery	Radical nephrectomy
Adjuvant Chemoradiotherapy	No
recurrence and metastasis time	6/25/2020
Chemotherapy for advanced stage	Navelbine+5-FU (six cycles, q3w)
Regimen after disease progression	Tislelizumab+arotinib
Disease progression	No
Efficacy evaluation	stable disease
Last follow-up time	3/15/2022

Discussion

RCC accounts for 80% to 90% of adult renal malignancy and is highly heterogeneous [8,9]. The most frequent RCC is CcRCC, accounting for about 75% [10]. The characteristic molecular biological alterations in CcRCC show abnormal expression of VHL genes and expression of vascular endothelial growth factor caused by HIF regulated gene transcription [11,12]. The recurrence pattern of CcRCC is mainly distant metastasis with poor sensitivity to chemoradiotherapy, and antiangiogenic agents represented by sunitinib; parazopani and capotinib are the first-line drugs for advanced CcRCC. The results of large clinical studies including IMmotion151, JAVELIN Renal 101 and Keynote 426 showed the

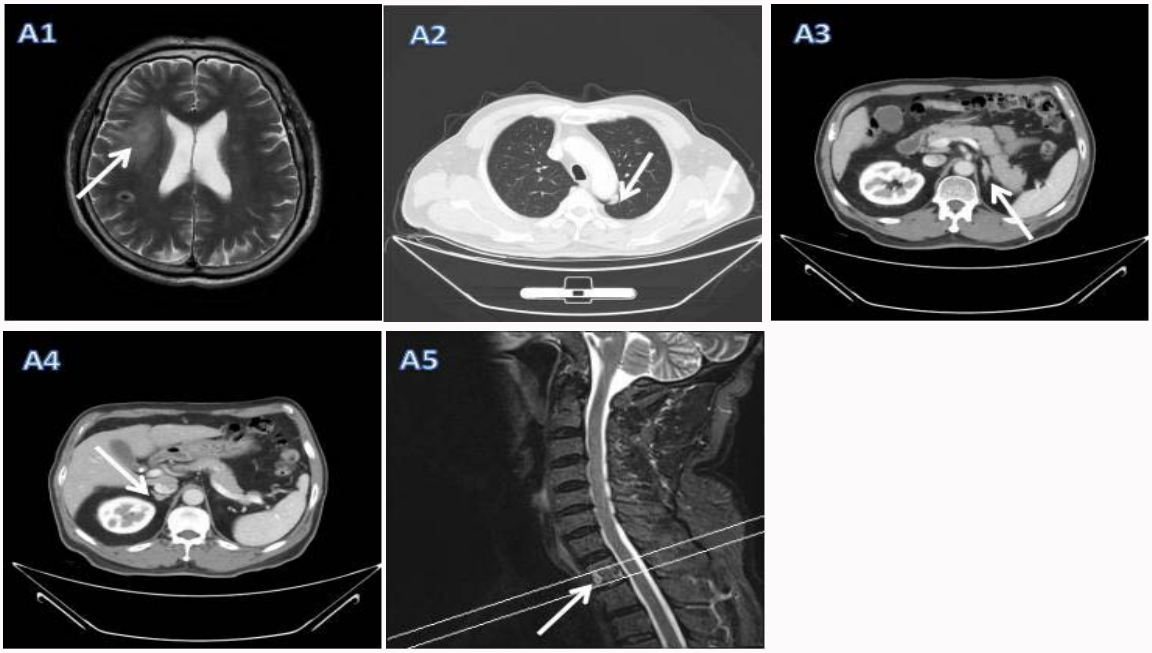

Figure 3: After 3 months of Tislelizumab combined with arotinib treatment, disease decreased and remained stable persistently. A1 brain metastasis, A2 left lung metastasis; A3 left adrenal metastasis, A4 right adrenal metastasis, A5 thoracic 1 vertebral metastasis.

Table 2: 26 phase III clinical trials of Tislelizumab registered.

NCT number	Number Enrolled	Conditions	Interventions	State
NCT05244798	360	ESCC	Tislelizumab+Chemotherapy/Tislelizumab+Chemoratiotherapy	Not yet recruiting
NCT05211232	450	NPC	Tislelizumab+Chemotherapy/placebo+Chemotherapy	Not yet recruiting
NCT03594747	360	NSCLC	Tislelizumab+Chemotherapy/Chemotherapy	Active, not recruiting
NCT04921358	420	NSCLC	Tislelizumab+Sitravatinib/Chemotherapy	Recruiting
NCT04799314	132	DLBCL	Tislelizumab/No intervention	Not yet recruiting
NCT04486391	123	CHL	Tislelizumab/Chemotherapy	Recruiting
NCT04789434	94	DLBCL	Tislelizumab/No intervention	Recruiting
NCT03663205	334	NSCLC	Tislelizumab/Chemotherapy	Active, not recruiting
NCT04746924	605	NSCLC	Tislelizumab/Pembrolizumab	Recruiting
NCT03745222	840	NSCLC	Tislelizumab+cCRT/placebo+cCRT	Terminated
NCT03924986	256	R/MNPC	Tislelizumab+Chemotherapy/Chemotherapy	Active, not recruiting
NCT04866017	900	NSCLC	Tislelizumab+ociperlimab/Durvalumab/Chemotherapy	Recruiting
NCT03967977	420	UC	Tislelizumab+Chemotherapy/Chemotherapy	Recruiting
NCT04005716	457	SCLC	tislelizumab+etoposide+platinum/Placebo+etoposide+platinum	Active, not recruiting
NCT04379635	450	NSCLC	Tislelizumab+Chemotherapy/placebo+Chemotherapy	Recruiting
NCT03783442	649	ESCC	Tislelizumab+Chemotherapy/placebo+Chemotherapy	Active, not recruiting
NCT03777657	997	GA/GEJA	Tislelizumab+Chemotherapy/placebo+Chemotherapy	Active, not recruiting
NCT03430843	513	ESCC	Tislelizumab/Chemotherapy	Active, not recruiting
NCT03957590	370	ESCC	Tislelizumab+Chemoratiotherapy/placebo+Chemoratiotherapy	Active, not recruiting
NCT03412773	674	HCC	Tislelizumab/Sorafenib	Active, not recruiting
NCT04164199	300	AM	Tislelizumab/Pamiparib	Enrolling by invitation
NCT05152147	714	GN/GEJA/EA	Trastuzumab/Zanidatamab	Recruiting
NCT05245474	111	LARC	Tislelizumab+Chemoratiotherapy/Chemoratiotherapy	Not yet recruiting
NCT04973306	176	ESCC	Tislelizumab+Chemoratiotherapy/placebo+Chemoratiotherapy	Not yet recruiting

NCT04170283	500	BCM	Zanubrutinib+Tislelizumab/Zanubrutinib	Enrolling by invitation
NCT03358875	805	NSCLC	Tislelizumab/Chemotherapy	Active, not recruiting

Note: ESCC: Esophageal Squamous Cell Carcinoma; NPC: Nasopharyngeal Carcinoma; NSCLC: Non-Small Cell Lung Cancer; DBCL: Diffuse large B-Cell Lymphoma; CHL: Classical Hodgkin Lymphoma; R/MNPC: Recurrent or Metastatic Nasopharyngeal Cancer; UC: Urothelial Carcinoma; SCLC: Small Cell Lung Cancer; GA/GEJA: Gastric, or Gastroesophageal Junction Adenocarcinoma; HCC: Hepatocellular Carcinoma; AM: Advanced Malignancies; GN/GEJA/EA: Gastric Neoplasms, Gastroesophageal Adenocarcinoma, Esophageal Adenocarcinoma; LARC: Locally Advanced Rectal Cancer; BCM: B-Cell Malignancies

effectiveness and safety of immune combined antivascular therapy in advanced CcRCC, and rewritten the diagnosis and treatment guidelines of advanced CcRCC [13-15].

Arotinib is an oral pan tyrosine kinase inhibitor, which can effectively inhibit tumor angiogenesis, tumor cell growth and induce tumor cell apoptosis. It has the characteristics of high efficiency, low toxicity and multi-target [16-18]. Zhang C et al. [19] found that anlotinib significantly inhibited the proliferation, clonal formation and migration ability of ACHN cells in the CcRCC cell lines, providing the rationale for the application of anlotinib in CcRCC. The Zhou et al. [20] found a significant increase in PFS in the second-line treatment of renal cancer compared with sorafenib and axitinib. Professor Ma Jianhui team of MRCC II clinical research results show that compared with sunitinib, anlotinib has non-inferiority, side effects. Yong found that arotinib was better tolerated than sunitinib and pazopanib, providing evidence-based medical evidence for the use of arotinib in the first-line and second-line treatment of MRCC [21,22].

Tislelizumab is a humanized IgG4 anti-PD-1 antibody independently developed by China. It avoids antibody-dependent cell-mediated phagocytosis. Compared with similar antibodies, it has an advantage of high affinity and minimal off-target effect [23-25]. Tislelizumab dissociates from PD-1 slowly and acts longer compared to Nivolumab and Pembrolizumab [26]. As of March 24th, 2022, a total of 180 registered clinical trials of tirelizumab were conducted in multiple countries and regions worldwide, with a total planned recruitment of more than 20 thousand patients, and 26 in phase III clinical trials (Table 2) [27]. The RATIONALE 001 study preliminarily showed the safety and efficacy of Tislelizumab in MRCC [28].

Targeted therapy combined with ICIs therapy is the first-line medium for CcRCC patients with IMDC medium and high risk, but drugs such as sunitinib, capotinib, pembrolizumab and avelumab are expensive and the medication use population is limited. Wu et al. [29] found that axitinib combined with Tislelizumab had a Disease Control Rate (DCR) of 80% and an Objective Response Rate (ORR) in patients with MRCC who failed first-line targeted therapy [29]. There is a case report showed the safety and efficacy of apatinib combined with Tislelizumab in the posterior line therapy of MRCC [30].

Advanced CcRCC with brain and lung metastases has an extremely poor prognosis. This case of advanced CcRCC patients with systemic metastases, large tumor load and poor economic conditions, cannot afford sunitinib, pembrolizumab.

After 2 cycles of vinorelbine combined with fluorouracil treatment, clinical symptoms improved. The lesions were significantly reduced after 4 cycles. Although the disease progressed after 6 cycles, it still showed the effectiveness of the chemotherapy regimen. The second-line of treatment of Tislelizumab combined with arotinib had brought great survival benefits to patients. 15 months of PFS has been obtained to date.

Conclusion

In this study, Tislelizumab combined with anlotinib inpatient with advanced CcRCC has achieved phased success, demonstrating the feasibility of this new treatment model. We envisage what it will present when chemotherapy Combined antiangiogenic drugs and immunotherapy are administered to the CcRCC patients as the first-line treatment method. Due to the limitation of clinical data, we will further explore the safety and effectiveness of this treatment model.

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