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Case Report

A Complete Response of Metastatic Renal Cell Carcinoma to Bevacizumab and Interferon after a Nephrectomy: Case Report

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Abstract

In general, metastatic renal cell carcinoma (mRCC) is managed with systemic treatments and cytoreductive nephrectomy is recommended only when it is feasible. Historically, systemic treatment of mRCC was limited to cytokine treatment with interferon (IFN) and interleukin (IL)-2, as chemotherapy was considered to be ineffective in these patients. Bevacizumab in combination with interferon alfa is approved for treatment-nave advanced renal cell carcinoma (RCC) in both the US and Europe. Its objective response rates is 30%. We report a case of a patient who presents a complete response after a nephrectomy and bevacizumab associated to interferon alpha.

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Introduction

Metastatic renal cell carcinoma (mRCC) has showed a resistance to chemotherapy and modest response to cytokine therapy [1]. Before the year 2000, high-dose interleukin-2 was the only drug that was approved by the U.S. Food and Drug Administration (FDA) for metastatic situation, with 10% longer duration of complete remission [2]. Interferon (IFN)-regimens have been used to treat metastatic RCC based on a survival advantage demonstrated in some studies [3].

The most common histologic variant, involving von Hippel-Lindau (VHL) tumor suppressor gene inactivation, has occurred. Normally VHL encodes a protein that is a component of a ligase for hypoxia-inducible factor (HIF). Under normal oxygen tension, ligase action inactivates HIF. Under hypoxic conditions, or with VHL inactivation, HIF upregulates the transcription of multiple hypoxia-inducible genes, including those encoding vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), epidermal growth factor receptor (EGFR), transforming growth factor-, and others that promote angiogenesis and cellular proliferation [4]. Other non-VHL pathways leading to RCC may share aberrant activation of the hypoxic response.

Approved therapies include inhibitors of VEGF and PDGF receptors (sunitinib and sorafenib) and mammalian target of rapamycin (mTOR) inhibitors (temsirolimus and everolimus) [5]. Most recently, the anti-VEGF antibody bevacizumab in combination with IFN was approved and is the subject of this case report.

Case Presentation

A 64 years old male presented with cough and chest pain, the pulmonary radiography revealed nodules and a computed tomography scan (CT scan) showed a voluminous renal tumor with pulmonary metastases and a cytoreductive nephrectomy was performed in August 2011 and pathology revealed a Fuhrman grade 3 clear cell adenocarcinoma of 9x8x7 cm with necrosis (**Figure 1**), a cerebral scan revealed 2 metastases (**Figure 2**).

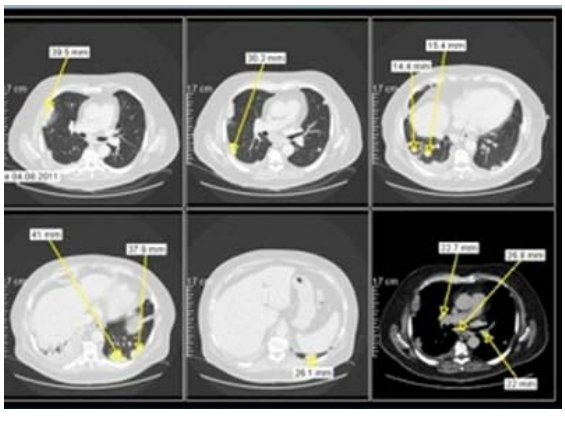

Figure 1 CT scan showed pulmonary metastases

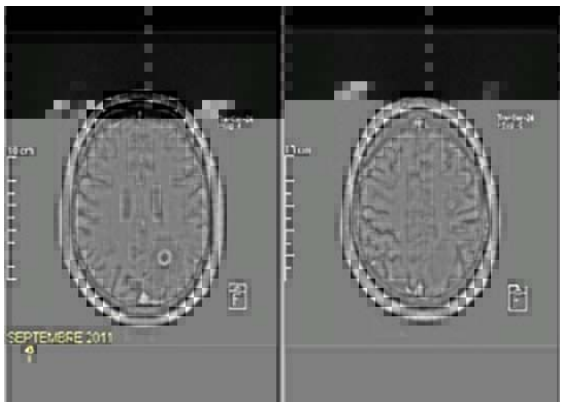

Figure 2 a cerebral scan revealed 2 metastases

After nephrectomy a significant pulmonary response is observed (**Figure 3**). Stereotaxic encephalic radiotherapy is done in October 2011with a significant control. Bevacizumab and interferon was started in November 2011 to April 2012 in the total of 12 cycles A complete response mediastino-pulmonary is observed in January and cerebral complete response in March 2012. In January 2012 interferon was stopped for toxicity asthenia grade 3 and in April 2012 bevacizumab was also stopped because the patient presented a heart failure with ejection fraction (EF: 48%) and a pulmonary arterial hypertension (PAH: 55+10mmHg) and decision was monitoring the patient every three months. The different CT scan and magnetic resonance imaging (MRI) confirmed the control of the metastatic disease (**Figure 4**). In June 2016 a modification of cerebral metastases was observed in favour of a late necrosis induced by the radiotherapy and that was treated with corticoids and anti-epileptic. The most recent CT scan and MRI revealed a persistence of the complete response with almost six years without any specific treatment of the cancer.

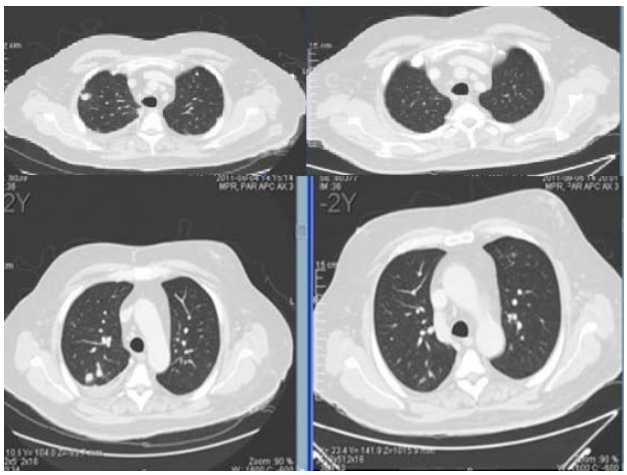

Figure 3. a CT scan showed a significant pulmonary response

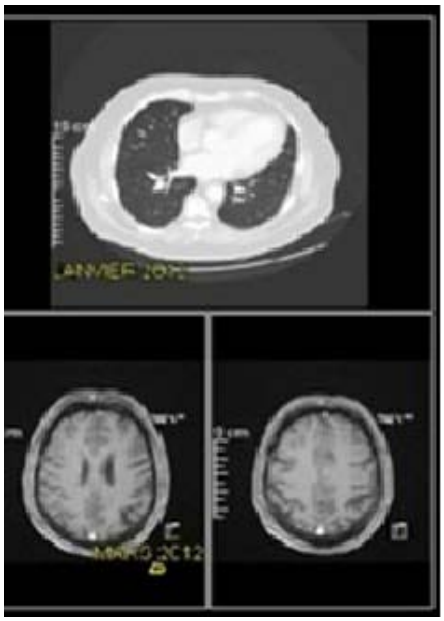

Figure 4. a CT scan and MRI confirmed the control of the metastatic disease

Discussion

The treatment of metastatic renal cell carcinoma (mRCC) has been developed in the objective of transforming cancer to a chronic rather than a lethal disease. This has been demonstrated with the advances in systemic therapy. mRCC is known to have low response rates to classic cytotoxic therapy, with more than 70 agents had been tested and response rates is under 10% [6]. The American Cancer Society stated kidney cancer comprises approximately 3-5% of adult malignancies in the United States with approximately 61,000 new cases diagnosed and over 13,000 deaths reported in 2011[7]. 25% to 30% of patients will present in metastatic stage and 25% to 30% are initially presented with localized disease will progress at sometimes [8].

The treatment of RCC consists on nephrectomy if localized case and medical treatment in the

metastatic case, a study showed that nephrectomy before interferon alfa-2b therapy for metastatic renal-cell cancer had a survival benefit. Metastatic renal-cell cancer is very difficult to treat effectively, because of its resistance to chemotherapy. Yagoda *et al*. reviewed a large series of trials of chemotherapeutic regimens and found a 5.6% rate of objective response to cytotoxic agents in 3502 treated patients [6]. There are, also, indications of improved survival with chemotherapy after nephrectomy [5], previous trials of biologic-response modifiers in metastatic renal-cell cancer have shown an improved response rate or improved survival after surgery of the primary tumor [3]. The interval from nephrectomy to the systemic treatment of the renal-cell cancer was not controlled in these series. The effect of nephrectomy may, however, be real. Several reports of immunotherapy for renal-cell cancer, with or without concomitant chemotherapy, have supported the idea that patients who undergo nephrectomy before systemic treatment have a survival advantage [8].

The CARMENA trial, phase 3, multicenter and randomized, started in 2009. Initiated by the French Association of Urology and the Getug (Study Group of Urogenital Tumors), it was piloted at the Institute of Gustave Roussy (Villejuif). A total of 450 patients were included in this trial. They were treated either by surgery then sunitinib, or by sunitinib alone. After a follow-up of approximately 4 years (51 months), overall survival was greater (more than 6 months) in the group treated with sunitinib alone than in the surgery. So in practice it will be possible to offer only and faster medical treatment for patients with metastatic tumors.

The place of palliative nephrectomy in monotherapy has been shown to be limited at present. Patients who present a poor condition, the surgery may lead to significant morbidity and mortality [9]. The indication for palliative surgery should be set in a symptomatic patient when the primary tumor is considered potentially unresectable and usual measures are insufficient to control the symptomatology [10]. In fact, palliative nephrectomy may not solve the specific problem which it was intended to palliate, given that the systemic effects may be caused by the metastatic diffusion rather than the primary tumor [7]. The QoL provided by palliative nephrectomy in selected patients may be seen improved when compared with other alternative strategies [8]. The combination of bevacizumab and interferon alfa is now approved for treatment-nave advanced renal cell carcinoma (RCC) in both the US and Europe. Its objective response rates of 30% and progression-free survival rates of 910 months are comparable to the other approved first-line multityrosine kinase inhibitors, sunitinib and pazopanib [10]. Bevacizumab (Avastin) is a humanized mAb that inhibits VEGF activity. It has significant clinical benefits in patients with the most common solid tumors, including metastatic colorectal carcinoma, metastatic breast cancer and non-small-cell lung carcinoma. Phase II trials demonstrated that bevacizumab has a moderate activity and is well tolerated in both groups patients therapy-naive and pre-treated mRCC[10]. Also, experience from clinical trials indicates that bevacizumab does not increase the toxicity of concomitantly administered chemotherapy [9]. Bevacizumab and IFN suppress tumor growth by direct and indirect mechanisms, and these two agents may have synergistic effects when are associated. Both agents have stimulatory effects on the immune response. For example, VEGF blockade, similarly to IFN treatment, has been shown to improve the function of dendritic cells [11], which is suppressed in advanced cancer as a result of VEGF-mediated inhibition [10]. Preclinical evidence also indicates that IFN has antiangiogenic activity [12] that is both dose and schedule dependent, with lower doses having greater antiangiogenic effects than 5-to 10-fold higher doses [9]. Until the middle of this past decade, immunotherapy with interleukin-2 (IL-2) or interferon-(IFN-) was considered to be the standard of care for mRCC. Response rates with high-dose IL-2 have been reported at 20%, and complete responses at 7% with a minority of patients achieving a durable response [13]. The toxicity profile of the association often limits its indication [14]. Most patients

receive a dose of 918 MIU (subcutaneous) , three times per week, but this regimen is associated with important toxicity, most frequently fatigue and influenza-like symptoms, also depression and asthenia [12]. Some side-effects (depression) are not dose related, several studies have demonstrated that IFN dose reduction leads to improve overall tolerability for patients with hepatitis C and mRCC[15]. This prospective randomized trial showed a greater OS in patients with metastatic clear cell RCC receiving bevacizumab plus IFN-as initial systemic therapy compared with IFN-alone. However, the clinical benefit of the addition of bevacizumab to IFN-is evident with prolonged PFS and increased objective response rate, as reported previously in this trial and in a similar phase III trial [10]. For patients with cerebral metastases there is an indication of stereotaxic radiotherapy especially for small tumors having size under 2 or 3cm with a significant control. And expected patient survival may be used to guide clinicians about proper treatment strategy . Generally patients with an expected median survival under 3 months should not be exposed to potential risks of surgery or stereotactic radiotherapy since the cost/benefit ratio of these treatment modalities is questionable in this group of patients.

The immune system to improve the prognosis for metastatic RCC has led to evaluation of several immune checkpoint inhibitors and vaccination strategies in multiple ongoing trials. The OS reported with the PD-1 inhibitor nivolumab in previously treated mRCC has already exceeded the median OS reported with IL2 in the first-line treatment of mRCC with manageable toxicities. Combinations of PD 1 inhibition with VEGF-TKIs and CTLA-4 inhibitors have shown significantly higher response rates. Meaningful clinical benefit has been observed with these checkpoint inhibitors in heavily pre-treated patients with mRCC. Immune checkpoint inhibitors under investigation include the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors, ipilimumab and tremelimumab; the programmed cell death protein 1 (PD-1) inhibitors, nivolumab (OPDIVO which is US Food and Drug Administration [FDA], approved), pembrolizumab, and pidilizumab; and the programmed cell death protein ligand 1 (PD-L1) inhibitors atezolizumab, durvalumab, and avelumab. This clinical case of the complete response to the association of Bevacizumab and IFN after a nephrectomy is probably a proof of immuno-sensitivity of renal cell carcinoma.

Conclusion

Bevacizumab associated to IFN has an FDA-approved option for first-line therapy in metastatic RCC. But this association is not refunded because of its low benefit. Additionally, cytoreductive nephrectomy is usually indicated before starting the systemic treatment in patients with metastatic disease.

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