Combination of Immunotherapy and Surgery in Metastatic Renal Cell Carcinoma

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ABSTRACT

Introduction and Objectives. Renal clear cell carcinoma (RCC) represented approximately 3% of all cancers diagnosed in Europe between 2018 and 2021, constituting approximately 90% of all malignant kidney tumors, with an annual increase of 2% in the incidence of RCC both worldwide. The updated European Association of Urology (EAU) guidelines recommend considering cytoreductive nephrectomy in patients who respond to initial immunotherapy (IO). The aim of this paper is to present the combination of immunotherapy and surgery in a RCC patient with venous thrombus, diagnosed in the metastatic stage.

Materials and Methods. We present the case of a 43 years old male patient imagistically diagnosed with 115 mm right kidney tumor with thrombosis of the ipsilateral renal vein up to the level of the inferior vena cava with multiple bone and pulmonary metastases, $cT_{3b}N_1M_1$. After ultrasound-guided renal biopsy revealed renal cell carcinoma Fuhramnn 2, the patient is referred to the Oncology department to initiate IO with nivolumab and ipilimumab, external radiotherapy with photons for the bone lesions, zolendronic acid and also anticoagulant treatment for the thrombotic extension. The main adverse effects of the IO were skin rash and autoimmune thyroiditis. Twenty four days after the final dose of the IO, cytoreductive nephrectomy, with lateral resection of the inferior vena cava, thrombectomy and lateral and retro-caval lymph node dissection through an anterior transperitoneal approach was performed, which was difficult due to the inflammation.

Results. Histopathological examination revealed residual RCC, ypT_{2a}, ypN_0 and the imagistic procedures after 6 months revealed an important reduction in size and number of the bone and pulmonary metastases. The therapeutic outcome of patients with mRCC have significantly improved with the molecular targeted agents, so prognostic models combining more independent factors have been developed to be more accurate than TNM stage or grade alone. More newly published studies talk about the difficulty increased surgery after immunotherapy due to the inflammatory reaction. The most common side effects of the IO are fatigue, skin toxicity, gastrointestinal toxicity and endocrinopathy, but although more than a half of patients experience treatment related toxicity, there are studies that support the fact that patients who experience severe adverse events, showed longer progression-free survival. Development of a novel risk score in order to find the optimal candidates for cytoreduction nephrectomy from the cohort of patients who can be classified as intermediate risk becomes of overwhelming importance.

Conclusions. The present case supports the idea that deferred cytoreductive nephrectomy, has the potential to exert a therapeutic effect in patients who obtain favorable response to IO for a certain period of time, but there must be taken in consideration the side effects of the IO and the increased difficulty of the surgery. Prospective randomized clinical trials are needed to confirm the prognostic impact of deferred nephrectomy in metastatic renal cell carcinoma after front line immunotherapy.

Key-words: renal clear cell carcinoma, venous thrombus, cytoreduction nephrectomy, immunotherapy

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INTRODUCTION AND OBJECTIVES

Clear cell carcinoma (RCC) represented approximately 3% of all cancers diagnosed in Europe between 2018 and 2021, constituting approximately 90% of all malignant kidney tumors, with an annual increase of 2% in the incidence of RCC both worldwide, and in Europe, with an estimated 39,100 kidney cancer-related deaths in the EU in 2021.[1]

In many phase III trials that included RCC patients with venous thrombus, immunotherapy (IO) with checkpoint inhibitors conferred an overall survival (OS) benefit and improved objective response rates (ORRs) and complete response (CR) rates over antiangiogenic therapy alone in the overall population.[2]

Based on latest trials, the updated European Association of Urology (EAU) guidelines recommend considering cytoreductive nephrectomy in patients who respond to initial treatment - a combination of immune checkpoint inhibitors with vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) for patients with metastatic clear-cell renal cell carcinoma, as in the new paradigm for the first-line therapy.

The role and the timing of cytoreductive nephrectomy (CN) is not well established yet. Previous retrospective studies of deferred CN reported that tumor shrinkage and reduction of neovascularization may facilitate the resection, but also suggested increased surgery-related adverse events when compared to untreated patients.[3] Taking into consideration prior trials, factors such as the presence of systemic symptoms, burden of extra-renal disease, and International Metastatic RCC Database Consortium (IMDC) risk might be able to guide the decision for CN in metastatic RCC.[4]

Although 30-50% of RCC patients with venous thrombus have metastatic disease at presentation, prospective data are limited evaluating OS following immunotherapy and CN in patients with tumor thrombus.[5]
The aim of this paper is to present the combination of immunotherapy and surgery in a RCC patient with venous thrombus, diagnosed in the metastatic stage.

MATERIALS AND METHODS

We present the case of a 43 years old male patient, investigated for pain in the left abdomen. After abdominal ultrasound (US) which raised the suspicion of a renal tumor, a contrast enhanced Computed Tomography scan was made. The CT scan revealed a right kidney tumor with a dimension of 115 mm with thrombosis of the ipsilateral renal vein up to the level of the inferior vena cava, osteolytic bone lesions at the level of the right femoral head with a size of 28 mm in length, other lesions at the level of the left iliac wing, at the level of the vertebral bodies T7 and T9 and also bilateral pulmonary basal nodular and macronodular lesions, $cT_{3b}N_1M_1$.

A bone scan was performed which documented multiple secondary lesions located at the level of: right antero-parietal cranial skull, left anterior costal arch I, thoracic vertebrae (T7, T9), pelvic bones (sacral S2/S3, left iliac crest extended acetabular) and coxo-femoral joints, with maximum dimensions at the level of the right femoral neck.

Ultrasound-guided renal biopsy was performed and the pathological examination revealed renal cell carcinoma Fuhrmann 2.

After evaluation, the patient is referred to the Oncology department where he was considered eligible for treatment with nivolumab and ipilimumab; external radiotherapy with photons was initiated, 3D-CRT technique, for the lesions at the level of the left iliac wing and also for the vertebral thoracal bodies (30 Gy in 10 fractions for each lesion); zoledronic acid therapy and also anticoagulant treatment for the thrombotic extension. There was a 9-day interval from diagnosis to initiation of systemic treatment, Karnofsky Performance Status (KPS) was 100%, laboratory testing demonstrated hemoglobin (Hgb), neutrophil count, platelet (Plt) count, calcium (Ca) within normal limits. IMDC score was 1 – intermediate risk.

The best treatment response was partial response (PR)[6], based on RECIST 1.1, achieved after 4 courses of immunotherapy (Nivolumab 3 mg per kilogram and Ipilimumab 1 mg per kilogram) followed by 4 courses of Nivolumab (480 mg).

IO was discontinued due to severe fatigue and a new skin rash on the face and posterior trunk without pruritus, adverse effect classified CTCAE 3 (Common Terminology Criteria for Adverse Events), which required postponing the administration of immunotherapy for 10 days. Another adverse effect occurred is autoimmune thyroiditis (CTCAE 2) - the hypothyroid phase, which is why substitution treatment is initiated.

24 days after his final dose of IO, the patient underwent cytoreductive nephrectomy, with lateral resection of the inferior vena cava, thrombectomy and lateral and retro-caval lymph node dissection through an anterior, transperitoneal approach. The surgery was technically difficult due to inflammation obscuring surgical dissection planes. The post-operative evolution was favorable, but with a late healing of the surgical wound, this requiring 30 days of post-operative care.

RESULTS

Histopathological examination revealed residual clear cell renal carcinoma, less than 5% of the tumor mass - major post-therapeutic histopathological response ypT_{2a}; group of 6 lateral and retro caval lymph nodes with sinus histocytosis ypN_0.

The CT examination performed 6 months after the initiation of the treatment revealed an important reduction of the metastasis at the level of the femoral head, the quasi-complete reduction of the secondary determinations at the level of the spine as well as the reduction of the size of the pulmonary metastases. The bone scan revealed multiple lesions at the level of the skull, spine (T7 and T9), costal arches, sternum, pelvis, right femoral head.

DISCUSSIONS

The therapeutic outcome of patients with metastatic cell carcinoma have significantly improved with the molecular targeted agents. Prognostic models combining more independent factors have been developed to be more accurate than TNM stage or grade alone for predicting clinically relevant oncological outcomes.

In metastatic disease, risk groups assigned by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) (initially created in the targeted therapy era) have been used in the majority of recent randomized trials, including those with immune checkpoint inhibitors (ICIs), and it is suggested to be used as preferred model for clinical practice by the EAU guidelines.[7] At the moment it includes 6 variables, more precisely, namely the time from RCC diagnosis to systemic therapy initiation, Karnofsky performance status (PS), anemia, neutrophilia, thrombophilia, and serum-corrected calcium and although we could say that it is one of the most important tools used for patients diagnosed with mRCC[7], the large proportion of patients classified as intermediate risk, and the heterogeneity of this group could constitute an important disadvantage. A possible improvement could be made by addition of a seventh variable like the presence of bone / liver metastasis although there is no conclusive evidence that one prognostic model is more accurate than another[8]. However, the quality of these prognostic models is considered to be insufficient regarding surgical prognosis prediction of metastatic renal cell carcinoma patients and, thus, requires further improvements.[9]

Immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) receptor and its associated cell-surface binding ligand (PD-L1) associated with tyrosine kinase inhibitor (TKI) axitinib demonstrated a 47% decreased risk of death from all causes ($p < 0.0001$), a 31% decreased risk of disease progression ($p < 0.001$), and a 24% higher objective response rate ($p < 0.001$) across IMDC risk categories in comparison with sunitinib monotherapy[10–12], and although the role of CN is not well established yet there are a number of retrospective reports demonstrating the benefit in a subset of patients undergoing IO – therapy, which may result in a significant OS[13] or even complete response.[14]

There are more and more newly published studies that talk about the difficulty of surgery following immunotherapy from a technical point of view, due to the difficulty in finding the dissection plans mostly caused by the inflammatory reaction surrounding the kidney and adjacent tissues, which leads to the extension of operating times and an important increase of perioperative complications, reason why patients should be referred to expert centers in order to reduce the potential perioperative morbidity.[10,15,16]

The molecular targets attacked in cancerous cells are also expressed in normal cells, fact that explains the different grades of toxicity, resulting from the disruption of normal cellular function. Although targeted molecular therapies have good toxicity profiles, some patients are sensitive to these drugs and can develop particular and severe toxicities.[17] The most common side effects identified included fatigue, skin toxicity, gastrointestinal toxicity, and endocrinopathy.[18] In our case the rash, the hypothyroidism, the hyperglycemic episodes and the delayed wound healing were attributed to immunotherapy but the immune related adverse effects were not associated with OS in patients treated with nivolumab plus ipilimumab as a first line of treatment.[19]

The prognostic impact of immune-related adverse events in metastatic renal cell carcinoma treated with nivolumab plus ipilimumab remains unclear, but although more than half of patients experience treatment-related toxicities, there are studies that support the fact that patients who experience severe adverse events, showed longer progression-free survival.[19]
Development of a novel risk score in order to find the optimal candidates for cytoreduction nephrectomy from the cohort of patients who can be classified as intermediate risk becomes of overwhelming importance. There are studies that propose Tumor-related (location and number of metastatic lesions) and patient-related (obesity and performance status) features to be taken into consideration when deciding about cytoreductive nephrectomy.[20]

CONCLUSIONS

The present case supports the idea that deferred cytoreductive nephrectomy, has the potential to exert a therapeutic effect in patients who obtain favorable response to immunotherapy for a certain period of time.

Surgery in metastatic renal disease following molecular targeted therapies, where nephrectomy and IVC thrombectomy is the appropriate approach, is technically much more difficult, reason why patients should be referred to expert centers in order to reduce the potential perioperative morbidity.

The adverse events associated with immunotherapy in metastatic renal carcinoma are distinct from those of cytotoxic chemotherapy but, although the prognostic impact of these events remains unclear, there is no evidence showing an impact to OS.

Prospective randomized clinical trials are needed to confirm the prognostic impact of deferred nephrectomy in metastatic renal cell carcinoma after front line immunotherapy.

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