Case Report

The Efficacy of Lenvatinib and Everolimus in Chromophobe-type Non–Clear-Cell Renal Cell Carcinoma: A Case Report and Literature Review

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Clinical Practice Points

- First- and second-line treatments for metastatic non–clear-cell renal cell carcinoma (nccRCC) are not extensively studied and based on the well-defined treatments for metastatic clear cell renal cell carcinoma (ccRCC).
- Lenvatinib and everolimus have been studied in patients with ccRCC and are now established second-line therapy.
- This case report describes the use of lenvatinib and everolimus in a patient with metastatic nccRCC, and resultant marked reduction in tumor burden.
- Although it has been studied in patients with ccRCC, additional trials evaluating lenvatinib and everolimus may confirm the efficacy of this treatment regimen in patients with nccRCC.

Clinical Genitourinary Cancer, Vol. ■, No. ■, ■-■
Keywords: Chromophobe, Everolimus, Lenvatinib, Non–clear-cell renal cell carcinoma, Treatment

Introduction

Renal cell carcinoma (RCC) makes up 3% of all malignant tumors.[1] The most prevalent RCC is clear cell renal cancer (ccRCC), which represents 75% of all renal malignancies. The remaining cancers are often collectively termed non–clear-cell RCCs (nccRCC). These nccRCCs consist of papillary RCC (15% of RCCs), chromophobe renal cell carcinoma (chRCC) (5% of RCCs), unclassified RCC (4% of RCCs), and minor subtypes (< 1% of RCCs).[2] Typically, RCCs are classified in this manner because histological subtypes have major differences in underlying molecular alterations, clinical presentations, long-term survival, and appropriate treatment selection.

Treatment for localized RCC is surgical excision with curative intent. Unfortunately, 25% of patients will present with metastatic disease,[3] and approximately 30% of all localized RCCs will develop metastases.[2] The behavior of chRCC is often indolent, but has a higher propensity for progression after surgery.[4] If RCC is inoperable or metastatic, systemic treatment is required to treat the disease.[3]

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Submitted: May 15, 2017; Accepted: May 16, 2017

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Treatments for metastatic RCC have evolved dramatically since the 1990s. Previously, high-dose interleukin-2 and interferon-alpha were first-line treatments for the disease.[3] However, a phase III randomized controlled trial in 2007 compared high-dose interferon-alpha with the tyrosine-kinase inhibitor sunitinib, and determined that sunitinib had a better response rate and a greater progression-free survival,[5] supporting the hypothesis that anti-angiogenic therapy was rational in ccRCC due to molecular changes. Since then, additional approved treatments for metastatic ccRCC are the vascular endothelial growth factor (VEGF) inhibitors, including other tyrosine-kinase inhibitors, such as pazopanib, or the monoclonal antibody bevacizumab in combination with alpha-interferon.[6,7] One exception includes patients deemed to have a poor prognosis. Those patients are typically treated with an intravenous mammalian target of Rapamycin (mTOR) inhibitor, temsirolimus.[8]

After progression on a VEGF-targeted therapy, approved second-line treatments include axitinib, and cabozantinib, and the oral mTOR inhibitor everolimus as a single agent or in combination with lenvatinib.[6,7] In addition, many trials are investigating immunotherapy check-point inhibitors, such as nivolumab, pembrolizumab, or atezilizumab. These treatments are antibodies against PD-1 and its ligand PDL-1, which promote T-cell activation and immune response against the tumor cells.[9]

Most of the phase III randomized controlled trials studying the systemic treatments for RCC evaluated only patients with ccRCC, and excluded patients with nccRCCs. The rationale for excluding patients with nccRCC from most of these trials include the limited

1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2017.05.017

number of patients with nccRCC and the perception that patients with nccRCC will not meet inclusion criteria for clinical trials. Therefore, there is no high-level medical evidence from randomized trials regarding how to treat this subtype of renal malignancies, and experiential data is used to guide salvage therapy.

Case Report

A previously healthy 52-year-old man presented to the emergency room with abdominal pain. A computed tomography scan of the abdomen and pelvis demonstrated diverticulitis and an incidental left renal mass measuring 14.5 × 14.0 × 12.2 cm. He underwent a sigmoid colon resection and a left radical nephrectomy. The sigmoid colon pathology demonstrated diverticulitis with abscess formation; however, the renal pathology revealed RCC, chromophobe type. Although the surgical margins were free of tumor, well-circumscribed tumor nodules with surrounding lymphoid aggregates were present within the peri-renal adipose tissue. He was diagnosed with resected metastatic chRCC. The patient did not undergo any systemic treatment, and chose to pursue frequent surveillance.

Seventeen months later, follow-up imaging demonstrated residual soft tissue in the left nephrectomy bed, concerning for recurrent disease. Imaging also revealed an expansile lucent osseous lesion in the right pubic ramus concerning for distant metastases with associated pathologic fracture. Biopsy of one of the osseus lesions confirmed metastatic chRCC. Due to the progression of his disease, he underwent 28 weeks of treatment with temsirolimus, which stabilized the tumor burden and decreased the number of bone metastases.

After prolonged stabilization, it was decided to undergo a treatment holiday from temsirolimus (25 mg IV weekly). Ultimately over the next year he developed right hip pain, and imaging demonstrated a growing right inferior pubic ramus mass with extension into the right quadratus femoris with abutment of the obturator internus and externus muscles. He was palliated with radiation therapy, and then completed 18 doses of nivolumab (289 mg IV biweekly) with ultimate progression of his disease. The follow-up imaging demonstrated an interval increase in size of multiple metastatic osseus lesions and the soft tissue mass in the renal fossa, and new endovascular metastases in the lungs. Therefore, he was started on lenvatinib (14 mg PO daily) and everolimus (5 mg PO daily) as third-line treatment. After 26 weeks of treatment, his bone disease was stable and his lung metastases and soft tissue in the renal fossa had decreased in size (see Figures 1 and 2). Importantly also no new disease has been observed since starting this combination regimen.

Discussion

No randomized trials have established a standard of care for patients with nccRCC, specifically chRCC. Therefore, treatment regimens for such patients are often based on clinical trials evaluating patients with ccRCC,[10] and the specific drug is chosen based on symptoms, high tumor burden, response to first-line therapy, and so forth.[11] There have been several trials that specifically evaluated patients with nccRCC. Sorafenib and sunitinib were specifically evaluated in patients with metastatic chRCC,[12] because the median progression-free survival of patients with ccRCC who received sunitinib was 6 months longer than that in patients who received interferon alfa.[5] In addition, the randomized trial leading to the temsirolimus approval contained 90 patients (17%) with nccRCC, and demonstrated overall survival was longer in the subset of patients with nccRCC compared with patients with ccRCC.[13] Therefore, many guidelines recommend consideration of temsirolimus as first-line therapy for metastatic nccRCC.[6,7,13]

However, more recently, the randomized phase II ASPEN trial specifically evaluated patients with metastatic nccRCC, and compared the efficacy of the mTOR inhibitor everolimus with the VEGF inhibitor sunitinib. Patients who received sunitinib had an increased progression-free survival when compared with everolimus.[14] This trial helps to elucidate which treatments should be

Figure 1 **(A) Computed Tomography (CT) Scan Performed on August 11, 2016, Demonstrates a Surgically Absent Kidney, and a Lobulated Soft Tissue Mass in the Left Renal Fossa Measuring 2.6 × 4.2 cm, Presumably a Site of Local Recurrence. (B) CT Scan Performed on March 19, 2017, Demonstrates the Lobulated Soft Tissue Mass, Which Is Decreased in Size (Measuring 2.7 × 1.8 cm) When Compared With the Previous CT Scan on August 11, 2016**