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Ablation of a Site of Progression With Stereotactic Body Radiation Therapy Extends Sunitinib Treatment From 14 to 22 Months

Introduction

Historically, chemotherapy for clear-cell renal cell carcinoma (ccRCC) has not been effective, and fewer than 25% of patients respond to cytokine therapy.[1-3] Recommended treatment for patients with advanced ccRCC includes molecularly targeted agents such as sunitinib, a kinase inhibitor that targets vascular endothelial growth factor and platelet-derived growth factor receptors.[4,5] A randomized phase III study established the benefits of sunitinib over interferon alfa, demonstrating an improvement in median progression-free survival (PFS) from 5 to 11 months and a 31% response rate.[6,7]

When a patient progresses on a systemic agent, the typical course of action is to switch therapies.[8] We present a patient with broadly metastatic ccRCC who experienced progression at a single site while receiving sunitinib. After 14 months of sunitinib treatment, stereotactic body radiation therapy (SBRT) to the progressing metastasis allowed the patient to continue on sunitinib for 8 additional months until progression.

Case Report

An 83-year-old man with a history of diabetes, hypertension, and transient ischemic attacks developed gross hematuria. An ultrasound revealed a large right upper pole renal mass. A computed tomography (CT) scan of the abdomen and pelvis and a chest x-ray were negative for both regional and distant metastases, and the patient underwent a laparoscopic radical nephrectomy. Pathologic studies showed an 8.5-cm ccRCC, Fuhrman nuclear grade 3, extending into the renal vein but not the inferior vena cava (pT3a, Nx by American Joint Commission on Cancer, seventh edition). Surgical margins were unaffected by tumor.

Surveillance imaging studies 3 to 5 months later revealed retroperitoneal, as well as mediastinal and hilar, adenopathy with lymph nodes measuring up to 5 cm in diameter. The patient was started on temsirolimus, which was selected because of a short interval from surgery to the development of metastases, low hemoglobin, and the presence of cardiovascular risk factors.

The patient tolerated temsirolimus well, with only minor fatigue and occasional epistaxis. However, after 6 months, temsirolimus was stopped because of worsening adenopathy and bone metastases. The patient was started on intravenous bisphosphonates and also underwent SBRT and vertebroplasty of a T12 bone metastasis.

Systemic treatment was then switched to sunitinib, which was generally well tolerated. Imaging studies 3 months later revealed significant improvement in retroperitoneal adenopathy and stable disease elsewhere. After two additional cycles, CT scans showed resolution of the retroperitoneal adenopathy and stability elsewhere in lymph nodes and bone metastases.

Fourteen months after initiation of sunitinib, a CT scan showed isolated progression of a right adrenal metastasis, which measured 2.8 cm (compare Figs 1A and 1B, arrows). Given otherwise stable disease and no new metastases, this lesion was treated with SBRT (60 Gy in five fractions) over the course of 12 days, during which time sunitinib therapy was paused. The patient did not experience any toxicity and was continued on sunitinib. Follow-up imaging studies revealed substantial regression of the right adrenal lesion (Fig 1C, arrow). Other lesions were stable, and the patient remained on sunitinib for another 8 months until further progression.

After 22 months of sunitinib treatment, there was progression in bone metastases, and the patient underwent palliative radiation therapy (RT; 8 Gy in one fraction) to a 2.3-cm humoral lytic lesion. The recommendation was made to switch therapies, but the patient relocated and rapidly declined, dying shortly thereafter at 86 years of age.

Discussion

When a patient develops new metastases or experiences progression in pre-existing ones while undergoing systemic treatment, the conventional approach is to switch to an alternative agent.[8] Tumor progression is viewed as an indication that the malignancy has developed resistance to the current anticancer agent. Several patterns of resistance to targeted therapy have been recognized, and resistance has been broadly divided into innate and acquired.[8] Innate resistance is characteristic of tumors that fail to respond at all to an agent, whereas acquired resistance reflects the acquisition of resistance over time. Traditionally, however, little distinction has been made regarding the extent of progression. In clinical trials and on the basis of RECIST criteria, growth of a single lesion may be sufficient to establish disease progression.[9] This approach does not consider heterogeneity of disease.[10,11] Each metastasis likely represents an individual subclone with shared, but also unique, mutations. Thus, heterogeneity in the response to a specific drug across different metastases likely reflects mutation and biologic heterogeneity, which has been well documented within primary tumors.[12,13] We propose that resistance be categorized not only on the basis of the timing of its acquisition, but also on the basis of extent of tumor growth. Thus, resistance patterns could be divided into generalized or isolated.

In cases of isolated resistance, focal approaches can be considered. In the past, local treatment options for metastatic RCC were largely limited to surgical metastasectomy.[14] However, metastasectomy has several limitations, including its morbidity and a need to hold systemic therapy until healing has occurred. While the patient is off of systemic therapy, the growth of other metastases is unchecked, and progression may occur. With the advent of SBRT, we now have the ability to effectively target individual metastatic sites with ablative doses of radiation, conferring a high degree of local control with limited morbidity, short recovery times, and minimal disruption in the administration of systemic therapy.[15-20] Although selection bias

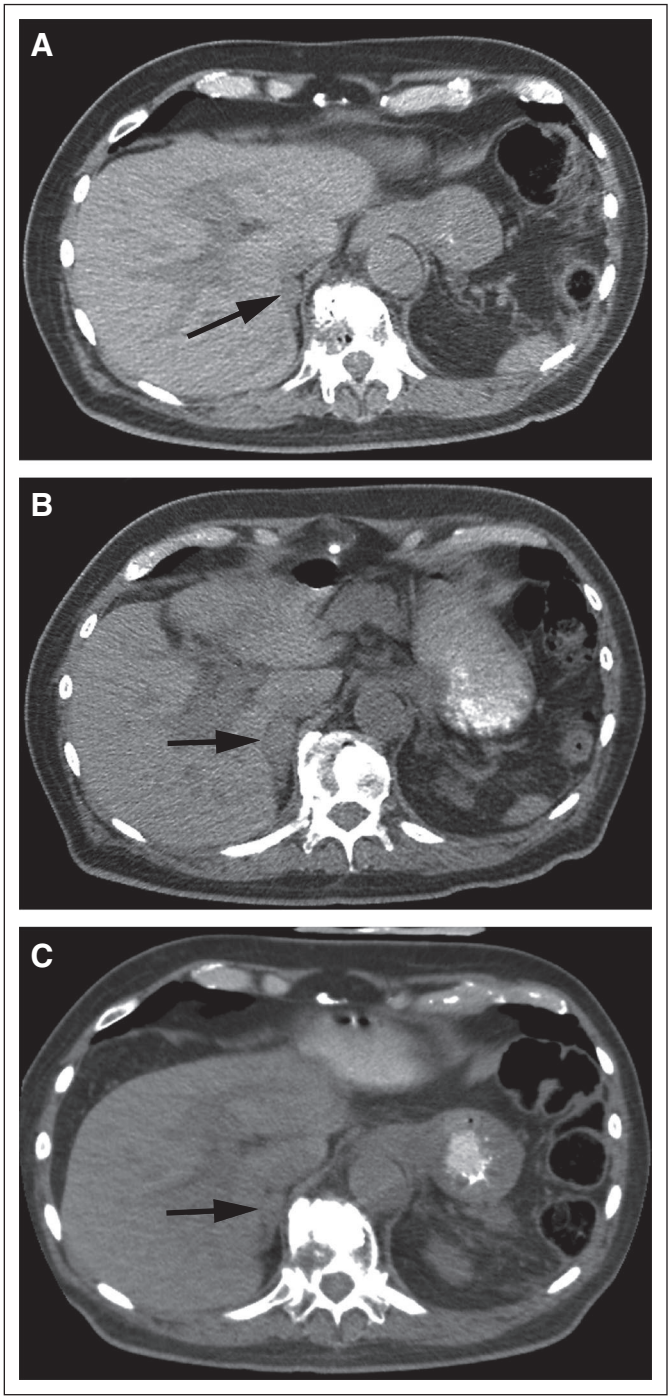

Fig 1.

may have influenced the results, several studies have demonstrated high rates of local control in sites treated with SBRT alone.[17-19]

There has been interest in combining systemic antiangiogenic agents and radiotherapy in the setting of oligometastatic disease. There are reports, including phase II studies of sunitinib and hypofractionated radiation therapy, suggesting efficacy and tolerability of such an approach.[21-24] However, when considering combined modality treatments, the potential for increased toxicity needs to be carefully considered. This may, in part, depend on the site of disease being treated, and different systemic agents may have different interactions with the various radiation treatments. For example, there are several case reports of gastrointestinal perforation with concomitant administration of standard doses of sorafenib (400 mg twice daily) and standard palliative RT (3 Gy × 10 treatments).[25,26] Both sorafenib and RT increase the risk of gastrointestinal perforation, and this effect may be magnified by their concurrent administration.[27,28] Before clinical trials establish the safety of concurrent approaches, the routine use of concomitant therapy for treatment of oligometastatic RCC cannot be recommended. However, sequential approaches of therapy may be considered, which may reduce the risk for overlapping toxicity of the two modalities while addressing both the systemic and local therapeutic needs of patients.

In summary, for patients who appear to be sensitive to a particular treatment (as determined by a prolonged progression-free interval), progression at a single site (or a few sites) may reflect the acquisition of resistance by a particular clone, and the administration of SBRT may extend treatment with a well-tolerated systemic agent. Whether this would improve patient overall survival needs to be determined. However, a similar approach of selective SBRT ablation of isolated, progressing sites in a few additional patients with ccRCC has shown promising results. Improved outcomes with the integration of focal therapies would result in a paradigm shift and would necessitate increased multidisciplinary collaboration in the treatment of patients with RCC.

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