

Prolonged Survival of a Patient With Papillary Renal Cell Carcinoma and Brain Metastases Using Pazopanib

Introduction

Renal cell carcinoma (RCC) accounts for 80% to 85% of primary neoplasms that arise in the kidney, with an estimated 65,000 new cases and 13,500 deaths each year in the United States.¹ Papillary RCC (PRCC) is the second most common type of RCC with a 5:1 male predominance.² PRCC is classified into two groups; type 2 tumors are high grade and associated with a poor prognosis.³⁻⁶

The prevalence of brain metastases (BM) from RCC ranges from 6% to 10%,^{7,8} and the reported median survival time is 5 months for patients who are treated with whole-brain radiotherapy (WBRT) alone.⁹ We present a patient who developed more than 20 BM plus multiple bone, lymph node, and soft tissue metastases roughly one decade after removal of the primary tumor, and who remarkably survived 23 months.

Case Report

In May 2010, a 74-year-old male presented with a cough and fever. A chest x-ray showed mediastinal adenopathy. Subsequent positron emission tomography and computed tomography (CT) scans revealed extensive cervical and mediastinal adenopathy. Magnetic resonance imaging (MRI) of the brain revealed more than 20 BM in the cerebrum and cerebellum. The two largest BM measured 2 cm in the left occipital lobe and 1.8 cm in the right frontal lobe. The remaining BM were smaller than 1 cm. The patient's only neurologic clinical finding was mild left hyperreflexia without weakness, and his Eastern Cooperative Oncology Group performance status was 0.

A lymph node biopsy showed RCC, which was consistent with the patient's history. The patient had undergone a left radical nephrec-

tomy in October 2001 for a localized RCC, and a 7.5-cm high-grade tumor extending into the perirenal adipose tissue (pT3a) was removed. In March 2003, he developed a 2-cm contralateral adrenal nodule. Continued image surveillance revealed stability of the right adrenal mass.

The patient was referred to the University of Texas Southwestern Medical Center for treatment. Because the specific RCC histology was unknown, arrangements were made to obtain the slides from the original resection that had occurred a decade earlier. Meanwhile, the patient began WBRT. He completed WBRT at the beginning of June 2010, having received 30 Gy delivered in 10 fractions. He tolerated the treatment well and started sunitinib 8 days after completing WBRT. At the end of June 2010, the radical nephrectomy pathology slides were reviewed internally and revealed PRCC type 2. The cells were similar to those from the lymph node biopsy, and the diagnosis of metastatic PRCC type 2 was established. At a physical examination at the end of the first cycle of sunitinib, an improvement was noted in his cervical and supraclavicular adenopathy. Therefore, sunitinib was continued.

However, a follow-up CT of the neck and chest in October 2010 revealed an increase in a conglomerate of nodal masses in the right supraclavicular area and worsening of the patient's right cervical adenopathy. Treatment was switched to everolimus. Everolimus, like temsirolimus, is a sirolimus analog, and its mechanism of action is indistinguishable from that of temsirolimus.¹⁰ By December 2010, the patient presented with superior vena cava compression, symptomatic right brachial plexopathy, and progression of the right cervical, mediastinal, and hilar lymph nodes. The patient's right neck and mediastinum were treated with hypofractionated intensity-modulated radiation therapy concurrently with everolimus, delivering 20 Gy in four fractions.

In January 2011, after intensity-modulated radiation therapy, systemic therapy was switched to pazopanib (800 mg per day). Continued imaging surveillance showed improvement extracranially and

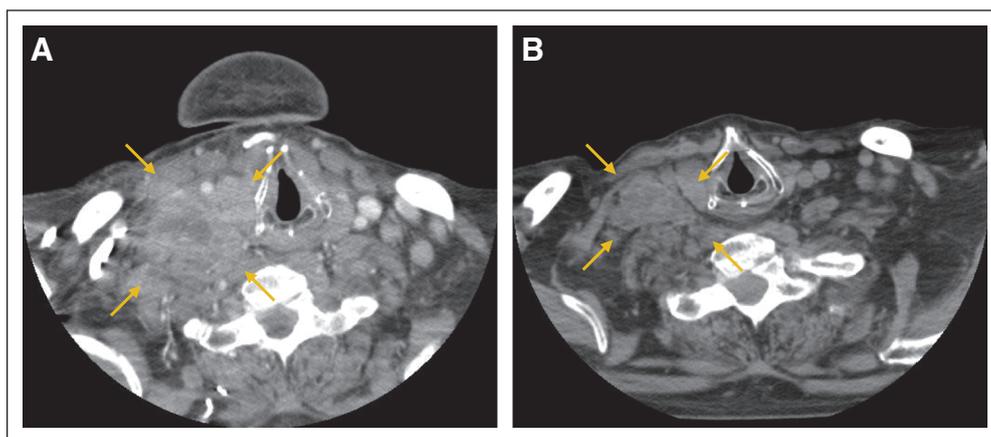


Fig 1.

stable BM. However, by the end of June 2011, a brain MRI scan revealed worsening intracranial disease with an increase in the number of lesions and progression in some preexisting metastases. At that point, pazopanib was discontinued and the patient started sorafenib.

Substantial disease progression took place throughout July 2011. CT scans revealed interval progression in the cervical lymphadenopathy, with extension into neuroforamina and the epidural space (Fig 1A, arrows). As determined by a brain MRI scan, BM continued to progress (compare Figs 2E and 2F with Figs 2C and 2D).

The patient had progressed on four lines of systemic therapy and we considered ceasing additional treatment. However, he was keen on exploring any available options. With progressive BM, clinical trials were not a possibility. Because extracranial disease had been controlled for 6 months with pazopanib, and considering

that the progression of BM may have resulted from low drug levels in the brain, we considered reinitiating pazopanib at an unconventionally high dose.

Pazopanib (1 g per day) was resumed in August 2011 along with prednisone (20 mg per day). A body CT scan and brain MRI scan in October 2011 revealed regression of cervical adenopathy (Fig 1B, arrows) and of several BM, with overall improvement in surrounding edema. In November 2011, the pazopanib dose was reduced to 800 mg per day because of high-grade palmoplantar erythrodysesthesia. Brain MRI scans in December 2011 and January 2012 showed overall stability in BM except for one hemorrhagic lesion. The patient's final brain MRI scan in March 2012 revealed no significant changes or new lesions (compare Figs 2E and 2F with Figs 2C and 2D).

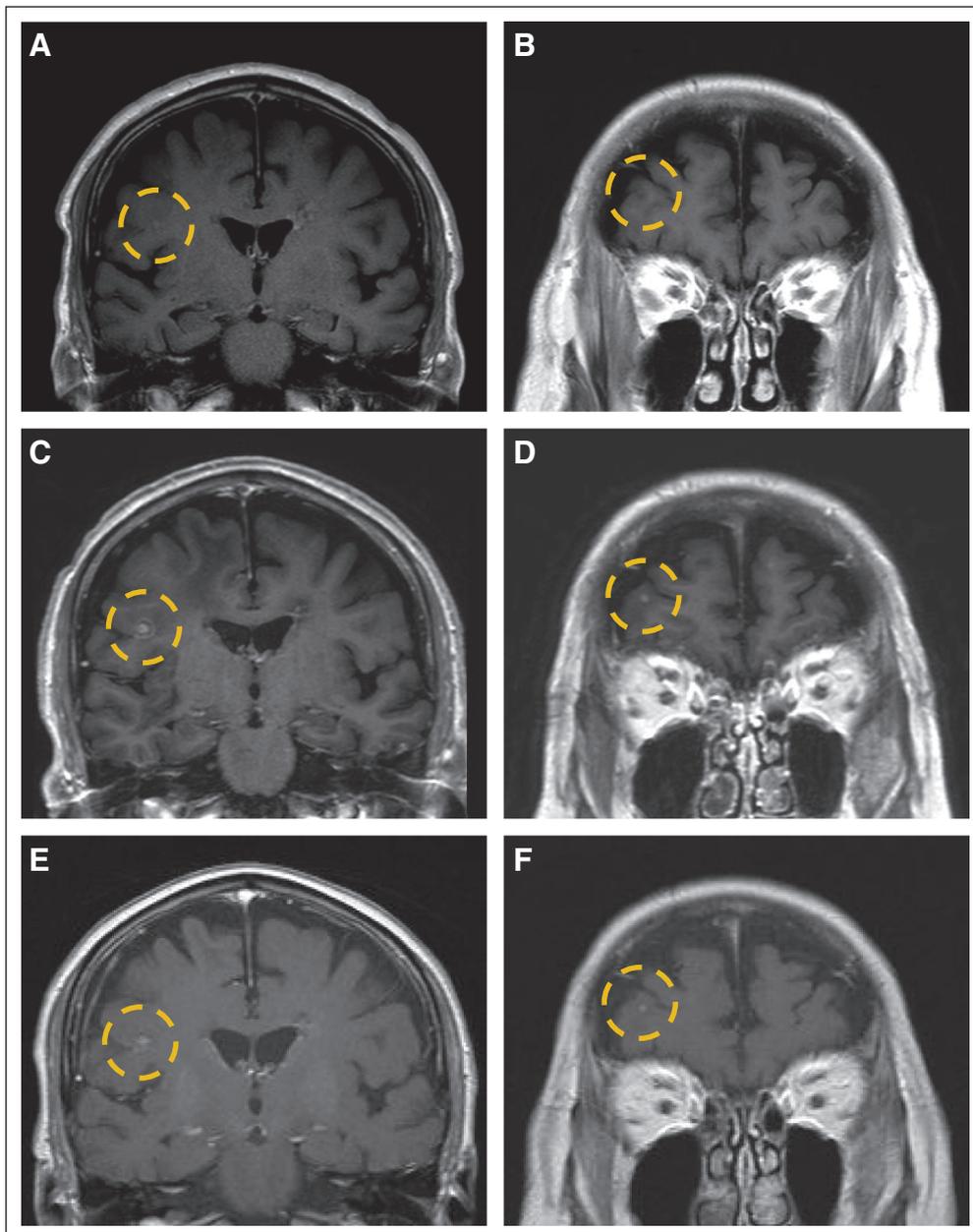


Fig 2.

In March 2012, the patient progressed to an Eastern Cooperative Oncology Group performance status of 4. This was attributed in part to prolonged corticosteroid therapy, and an attempt to taper the corticosteroids failed. Pazopanib was discontinued and shortly thereafter, in April 2012, the patient died. The patient had a remarkable survival of 23 months after his widely metastatic presentation.

Discussion

PRCC type 2 infrequently metastasizes to the brain.^{11,12} When a patient with PRCC type 2 develops BM, the prognosis has traditionally been dismal.^{13,14} The prognosis is worse when multiple BM are present.¹⁵ One retrospective study found a significant difference in overall survival among 119 patients with PRCC who were treated with WBRT alone depending on whether they presented with multiple BM versus a single brain metastasis ($P < .043$).¹⁶ The same investigators also found the leading causes of death to be neurologic (76%) and systemic (16%).¹⁶ However, other reports indicate that death as a result of intracranial disease progression was far less common (4% to 12%) than death as a result of extracranial disease progression (69% to 83%) in patients with metastatic RCC who were treated with radiation.^{17,18}

This patient's history is remarkable for a presentation with more than 20 BM 9 years after resection of a primary tumor and his extended survival. On the basis of other series, median survival is expected to be 3 to 5 months,^{9,16} yet this patient survived 23 months.

What accounts for this patient's extended survival? Tumor biology is certainly one possibility. Although the patient presented almost a decade later, which perhaps suggests smoldering disease, the disease burden and rapid progression on several lines of therapy suggests aggressive disease. This patient lived long enough to see intracranial progression after WBRT, which has not always been the case historically, given that patients die too early as a result of systemic disease.

Interestingly, the patient had a good response to pazopanib. For 6 months the patient was receiving the standard dose of pazopanib (800 mg per day) and then was switched to sorafenib for 6 weeks and experienced significant disease progression. Given that both sorafenib and pazopanib target vascular endothelial growth factor receptor 2 and platelet-derived growth factor receptor β ,¹⁹ but only pazopanib was active, these data suggest that the effectiveness of pazopanib may be attributed to the inhibition of another kinase or a result of improved bioavailability of this compound. Because of the previous prolonged extracranial disease control and minimal effects on quality of life, the patient was again prescribed pazopanib, but this time at a dose of 1 g per day. Pazopanib was increased with the hope that higher levels might increase brain penetration and result in the control of BM (BM were the main reason for its previous discontinuation). In addition, there is a precedent with other targeted agents with respect to improvements in outcomes with drug titration.²⁰

Figure 2 tracks two BM over time (indicated by gold circles). Figures 2A and 2B were taken after WBRT and before starting low-dose pazopanib; Figures 2C and 2D were taken after disease progression and before administering high-dose pazopanib; and Figures 2E and 2F were taken 5 months after initiating high-dose pazopanib. There was a clear progression in both lesions after the patient took the standard dose of pazopanib and sorafenib (compare Figs 2A and 2B with Figs 2C and 2D). Both metastases stabilized after administering the higher dose of pazopanib (Figs 2E and 2F).

Intracranial pazopanib response is an intriguing hypothesis but remains speculative with limited data. One case series found that

patients with RCC who had small asymptomatic supratentorial metastases without hemorrhage or herniation responded to sunitinib as initial therapy.²¹ Other case reports also suggest beneficial BM response to sunitinib.²²⁻²⁴ Animal studies have indicated that sunitinib²⁵ and pazopanib²⁶ indeed penetrate the blood-brain barrier. Also, a phase II trial of pazopanib showed evidence of CNS biologic activity in glioblastoma.²⁷ However, clinical relevance of these findings remains controversial, and our recommendation is not to administer antiangiogenic agents for BM unless they have been previously irradiated.

This patient report raises several interesting questions. First, does pazopanib have activity against PRCC, and should its role in this disease be systematically explored? Second, for patients who can tolerate it, would higher doses of pazopanib be more effective? Third, when a drug with brain penetration is active in controlling extracranial disease, but less so with respect to BM, should an increase in dose be considered?

In summary, we present a patient with metastatic PRCC who had a prolonged survival with pazopanib despite presentation with extensive BM. When faced with the option of hospice care, he elected to pursue a trial of an unconventionally high dose of pazopanib, which gave him an additional 7 months of tumor response and quality of life.

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