Intracranial metastases are the most common intracranial neoplasm, with an estimated yearly incidence of 200,000 cases, arising in 20–40% of all cases of systemic cancer. Lung, breast, and renal carcinomas represent the most common sources of metastases to the brain. It is estimated that nearly one-third of patients with RCC will have metastases at the time of initial presentation, and that 5–10% of all cases of RCC will metastasize to the brain during the course of the disease.9 Although RCC is considered relatively radioresistant to traditional fractionated radiation delivery, current treatment algorithms for RCC consist of radiation therapy and/or radiosurgery in combination with resection and systemic chemotherapy. Despite aggressive treatment with a combination of modalities, the prognosis for patients with RCC with cerebral metastasis remains poor, with a mean survival time of only 9.5 months.1 Breast cancer is the second most common source of brain metastases. Approximately 10–20% of patients with breast cancer will develop a metastasis to the brain, and the median time from initial diagnosis to detection of brain metastasis is nearly 3 years. Although traditionally thought to be more susceptible to radiation than RCC, similar treatment options are used in the management of RCC and breast cancer brain metastases. After a diagnosis of brain metastasis, the median survival time in patients with breast cancer is 5.6 months with only 23% of patients surviving longer than 1 year.9

Careful long-term follow-up for cerebral metastasis is needed in all patients with RCC and breast cancer because metastases are common and can present in a delayed fashion. When intracranial metastatic disease is detected, management often requires a multidisciplinary approach including surgical, radiation oncological, and medical oncological considerations. Systemic therapies for these conditions may influence the assessment and treatment of intracranial disease, and neurosurgical oncologists should be aware of potential interactions in treatment strategies.

The poor prognosis with advanced-stage RCC has led to increased interest in the development of novel chemotherapeutic agents for treatment of this tumor. Both sorafenib and sunitinib are multitargeted tyrosine kinase...
inhibitors that have been shown to inhibit growth of both tumor cells and tumor vasculature. Receptor tyrosine kinases play a role in the tumor angiogenesis via inactivation of the von Hippel-Lindau tumor suppressor gene, which regulates the production of hypoxia-inducible proteins, such as VEGF and PDGFR.7

Sorafenib (Nexavar; Bayer Pharmaceuticals Corporation) is an oral kinase inhibitor that targets tumor cells and the tumor vasculature. Although originally developed to inhibit Raf-1, a member of the Raf/MAPK/ERK signaling pathway, sorafenib has subsequently been found to have activity against multiple tyrosine kinases, including B-Raf, multiple VEGF receptors, PDGFR, Flt-3, c-KIT, and RET tyrosine kinases.15 Phase II trials have demonstrated antitumor effects in hepatocellular carcinoma, sarcoma, and RCC.14 A Phase III clinical trial demonstrated a significantly prolonged progression-free survival that was nearly double in comparison with a placebo group.9

Sunitinib (Sutent, Pfizer, Inc.) is also an oral, multitargeted tyrosine kinase inhibitor that has been shown to selectively block VEGFR Types 1–3 and PDGFR Types α and β, and c-KIT.31 Phase III trials have shown significant benefit for patients with RCC or gastrointestinal stromal tumors.5,12,13 There are additional Phase II trials reported for non–small cell lung cancer, neuroendocrine tumors, and breast cancer.1

Methods

We describe 4 cases of novel adverse effects resulting from the use of sorafenib and sunitinib, with reversible clinical and/or imaging changes on MR imaging. Four patients who had undergone previous surgery or radiosurgery for intracranial metastatic disease, with subsequent stable intracranial disease, demonstrated a reversible increase in contrast enhancement and peritumoral edema on brain MR imaging related to the use of sorafenib or sunitinib.

This study is derived from a prospective database for the identification and treatment of intracranial neoplasms at Penn State Hershey Medical Center and Penn State Cancer Institute. We identified 4 patients with metastases to the brain secondary to advanced RCC or breast carcinoma treated with either sorafenib or sunitinib between July 2005 and December 2007. In each case, sorafenib or sunitinib was given as a second-line agent for progressive or intractable systemic disease following surgical or radiosurgical treatment of a metastasis to the brain. Clinical history and imaging findings, both before and after initiation of the chemotherapy agent, are reviewed.

Case Reports

All 4 patients showed changes in Gd enhancement and/or T2-weighted or FLAIR imaging characteristics on brain MR images obtained after the administration of sorafenib or sunitinib. Three patients experienced clinical deterioration with respect to neurological symptoms or objective examination. At the time that the imaging changes and clinical deterioration were noted, all patients were started on corticosteroid therapy with a modest improvement in their clinical situation. However, steroids alone did not lead to a rapid clinical improvement or reversal of imaging changes. All of the patients underwent conservative, nonoperative management with careful clinical and radiographic follow-up. The clinical and imaging findings were reversible and improved after the drug was discontinued.

Case 1

This 53-year-old man presented with Stage IV RCC. He had previously undergone a right nephrectomy and right lower lung lobectomy for his primary disease and metastasis. He subsequently underwent treatment with systemic IL-2 with good disease control for 3 years. However, after that period he began to suffer from headaches and vertigo and was found to have right homonymous hemianopsia on clinical examination. Brain MR imaging demonstrated a single 3.5-cm-diameter, left occipital metastatic lesion that was resected without complications. Following surgery, the patient received whole-brain radiotherapy without chemotherapy. Surveillance brain MR images demonstrated stable postoperative changes in the region of the resection with no evidence of recurrent local disease for > 2 years. After ~ 2 years of systemic surveillance and treatment, this patient was found to have progression of his systemic disease unresponsive to IL-2 therapy and was started on sorafenib.

During the year after initiating sorafenib therapy, clinically progressive seizures developed with occasional breakthrough seizures despite anticonvulsant therapy. His family also reported episodes of confusion and behavioral changes described as periods of unresponsiveness, slowed cognition, and impaired recall from his previous baseline, which worsened while receiving cycles of sorafenib therapy and gradually improved to his baseline over the interval between cycles. No changes were observed on MR imaging until ~ 9 months after the initiation of sorafenib therapy. Clinical symptoms at this point were thought to be secondary to fatigue associated with chemotherapy cycles, and new-onset seizures were attributed to his previous craniotomy and tumor resection. Serial MR images showed increasing enhancement locally at the previous surgical site (Fig. 1). Magnetic resonance perfusion imaging and spectroscopy showed decreased regional blood flow and nonspecific neuronal loss without evidence of tumor progression, respectively. Recommendations were made for sorafenib to be discontinued; however, the medical oncologists were not convinced that the imaging changes did not represent disease progression.

The patient’s dose was reduced, and the amount of contrast enhancement seen on MR images diminished. However, during this time of reduced-dose sorafenib refractory seizures developed that progressed to status epilepticus and required hospitalization for treatment. At this time, the decision was made to stop sorafenib. Over the next few weeks he became seizure free on a 2-medication anticonvulsant therapy. His MR images continued to show progressive improvement on serial images, and his mental status improved to his pre-sorafenib therapy baseline.
Brain MR imaging after chemotherapy

Case 2

This 79-year-old man had a history of RCC with metastasis to the thyroid gland. He had previously undergone a left nephrectomy and thyroidectomy. Due to systemic disease progression, he was considered for further chemotherapy and underwent restaging. Magnetic resonance imaging of the brain revealed a single, asymptomatic right medial frontal lesion that was treated with Gamma Knife SRS. Three months after SRS, the patient was started on sunitinib for systemic disease control.

There were no clinical changes in his neurological examination or functional status. Two months after SRS, surveillance MR images demonstrated enlargement of the lesion, thought to be due to early radiation effect, with an area of central necrosis and a small amount of increased enhancement. The enhancement and edema improved by the time sunitinib therapy was initiated, although the relative size of the lesion increased secondary to central necrosis at 3 months after SRS. Follow-up MR images obtained 6 months after initiation of sunitinib showed increased enhancement and edema in the area of the lesion. Magnetic resonance spectroscopy and perfusion studies showed no evidence of tumor progression or elevated regional blood flow. Sunitinib chemotherapy was subsequently discontinued, and MR images obtained 3 months later demonstrated a significant reduction in the enhancement previously noted in the tumor area (Fig. 2).

Case 3

This 69-year-old man presented with progressive left upper-extremity weakness and a single focal motor seizure. His family had noticed some minimal cognitive slowing over the previous month. On examination, he was found to have mild monoparesis and mild ataxia. Magnetic resonance imaging showed 2 right hemispheric lesions deep within the white matter with significant vasogenic edema. Body imaging for systemic disease workup showed a large renal mass on the right side. The cerebral lesions were treated with SRS alone before the patient underwent partial nephrectomy for a 6-cm renal primary tumor. His left hemiparesis persisted with antigravity strength proximally and more impaired distal function. These interventions were completed prior to initiation of systemic IL-2 therapy. When his systemic disease progressed and became resistant to IL-2 therapy, the patient was started on sorafenib 15 months after SRS.

The patient and his family noted an early decrease in strength in his left arm and leg, as well as more difficulties...
walking after sorafenib therapy had been initiated. His proximal arm strength decreased to less than antigravity strength, and he became dependent on a walker for ambulation. Repeat imaging at 1 month after sorafenib treatment had been started showed increased peripheral enhancement and peritumoral edema, although MR spectroscopy and MR perfusion again provided evidence against tumor progression (Fig. 3). A recommendation was made to discontinue the sorafenib. Serial imaging follow-up after cessation of sorafenib showed progressive improvement of both the enhancement and edema. Clinically the patient showed slow progressive improvement in his hemiparesis and regained antigravity strength in his proximal arm without further intervention, although his ambulatory function never fully returned to the pre-sorafenib level.

Case 4

This 51-year-old woman with a known metastatic breast carcinoma to brain was referred to our institution for a second opinion. She had previously undergone mastectomy followed by chemotherapy and radiation to the chest wall and axilla with stable disease for 2 years. The development of headaches resulted in an MR imaging scan showing frontal metastasis. This frontal lesion was treated with resection followed by whole-brain radiation therapy. Local tumor recurrence 1 year later led to re-resection and Gliadel wafer implantation (MGI Pharma). Her CNS disease had been stable over the previous 8 months as documented on serial MR imaging. Approximately 8 months after surgery, metastases to the hip and liver were found. This systemic progression led to trial therapy with sunitinib, which was stopped after 5 weeks because of bone marrow suppression. She began treatment with another chemotherapeutic agent to address her systemic disease progression.

At this time she was referred to us for evaluation of suspected progressive metastatic brain disease. Her symptoms were stable but routine surveillance MR images demonstrated a slight increase in the enhancement and edema in the region of her tumor compared with images acquired 3 months earlier (Fig. 4). Magnetic resonance images obtained 1 month after cessation of sunitinib therapy without any further intervention demonstrated partial resolution of the enhancement and a more pronounced improvement in the perilesional edema. Further imaging follow-up could not be pursued as she progressed to palliative care because of systemic disease progression.

Discussion

Sorafenib and sunitinib have shown promising results as second-line agents for treatment of metastatic RCC systemically and have recently been approved for
Brain MR imaging after chemotherapy

Fig. 3. Case 3. One month after SRS (A) only a small amount of remaining enhancement was seen in the area of the tumors. One month after sorafenib treatment was started, an increasing amount of enhancement (B) was seen, and an area of diminished blood flow was seen on an MR perfusion study (C). Images obtained 6 (D) and 12 (E) months after treatment cessation demonstrate slow resolution of enhancement.

this indication. Due to their relatively new status, complete effect profiles on all systemic organ systems have not been well documented. We have seen what appears to be a potential adverse effect of these agents on the CNS in patients who have undergone a previous intervention for metastatic disease.

The reported side effects of sorafenib in the Phase III clinical trial included diarrhea, rash, fatigue, hand-foot skin reactions, and more rarely, hypertension and cardiac ischemia.\textsuperscript{4} Symptomatic toxicity was somewhat more common in sunitinib, with diarrhea, hypertension, hand-foot syndrome, myelosuppression, and decreases in left ventricular ejection fraction.\textsuperscript{1,12,13}

There has been a report of 1 patient with RCC without brain metastasis who developed symptoms of cortical blindness, seizure, and hypertension, with symmetrical, subcortical, bilateral occipital and parietal hyperintensity on T2-weighted images that was consistent with a reversible posterior leukoencephalopathy syndrome.\textsuperscript{10} This syndrome has been described in hypertensive encephalopathy and has been associated with immunosuppressive agents, cytotoxic drugs, and more recently bevacizumab (Avastin; Genentech, Inc.) and sorafenib (in a patient with cholangiocarcinoma).\textsuperscript{6} These 2 reported patients both presented with systemic hypertension and did not have any Gd enhancement on imaging.

We hypothesize that the increased peritumoral edema and enhancement result from leakage of the drug across a BBB that is already impaired from previous surgical or radiosurgical intervention. Drug leakage into the surrounding brain may potentially contribute to an inflammatory effect, resulting in enhancement and edema and at times causing clinical sequelae.

Alternative mechanisms may relate to the frequent side effect of hypertension caused by the drugs’ intracellular action against tyrosine kinase domains, or its extracellular antiangiogenic action against VEGFR, contributing to vasogenic edema via toxic insult to the BBB or vascular endothelium. These mechanisms may better explain the posterior leukoencephalopathy syndrome.

The lack of increased blood flow noted on MR perfusion studies argues against these as a significant relationship to hypertension, which was not a significant concern on review of the patients’ inpatient and outpatient charts.

Biochemical studies demonstrate that tyrosine kinase inhibitors have a mixed ability to cross intact BBBS.\textsuperscript{2,3} There may be a dose-response relationship in which patients with metastases to the brain could require a lower systemic dose to decrease the concentration in regions where significant enhancement indicates BBB disruption. The diffusion profiles of sorafenib and sunitinib across the BBB have not been studied.

The Penn State Cancer Institute is part of a central Pennsylvania cancer management consortium in which many patients receive some or all of their care at the Penn State Cancer Institute. Unfortunately, detailed records of care given outside the institution are frequently unavailable, particularly in patients traveling great distances for
only part of their evaluation and/or treatment. Due to the arrangement of this mixed central and local cancer care model, it is not possible to accurately determine the “denominator” from which these 4 patients were drawn. We were therefore unable to determine how many patients who had undergone previous SRS or resection later underwent either sorafenib or sunitinib treatment. Similarly, it is possible that these imaging changes occurred in other patients whose brain images were not reviewed at Penn State Hershey Medical Center and were misinterpreted as disease progression elsewhere. There were no other patients who had undergone surgery or radiosurgery at Penn State Hershey Medical Center who were later treated with either sorafenib or sunitinib.

Although no patient in this small case series underwent surgical decompression or biopsy sampling for pathological determination of the disease status/progression, in all 4 cases the temporal association with the improvement of clinical and/or radiographic findings coincided with the cessation of either sorafenib or sunitinib. This suggests that the clinical and MR imaging changes did not represent either cancer progression or recurrence.

Increased enhancement on MR imaging studies in the first months after SRS or Gliadel implantation may be misinterpreted as progression of disease. Only the second patient in this report demonstrated this “pseudo-progression,” which had regressed by the time sunitinib was started. The imaging characteristics described in this report were clearly separate from these initial findings. In each of the remaining 3 cases, the respective chemotherapeutic agent was not started until at least 8 months after SRS, resection, or Gliadel placement.

**Conclusions**

Following the administration of sorafenib or sunitinib, reversible MR imaging changes and clinical effects may occur, and these effects may be misinterpreted as progression of disease leading to inappropriate treatment plans. Recognition of these changes is critical so that misinterpretation and unnecessary treatment can be avoided and the offending agent discontinued.

**Disclaimer**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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