How We Treat Brain Metastases in Metastatic Renal Cell Carcinoma

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Overview

- Brain metastasis in patients with metastatic renal cell carcinoma generally signifies a poor prognosis.
- Surgical resection is an option for patients with a single metastasis and good extracranial disease control. Stereotactic radiosurgery is an option for patients with limited-volume brain metastasis, whereas patients with more widespread disease require whole-brain radiotherapy.
- Vascular endothelial growth factor receptor tyrosine kinase inhibitors have limited activity in brain metastasis related to renal cell carcinoma, although the activity of cabozantinib requires exploration.
- Preliminary studies suggest that newer immuno-oncology therapies such as nivolumab may have central nervous system activity in patients with brain metastasis from renal cell carcinoma.

Introduction

An estimated 64,000 new cases of kidney cancer were diagnosed in the United States in 2017, with approximately 14,400 deaths.[1] Most kidney cancers are renal cell carcinomas (RCCs) and originate in the renal cortex (80%-85%); the histologic type is predominantly clear cell (70%-80%). RCCs with a histologic type other than clear cell, such as papillary (10%-15%) or chromophobe (5%), are less common. RCC is typically local at presentation (65% of cases), but patients may also present with *synchronous* regional or distant metastasis (35%). *Metachronous* metastasis will develop in approximately one-third of patients in whom RCC is initially local. Sites of distant metastasis include the lungs, lymph nodes, liver, bones, and brain.[2] Numerous management options are available for patients with metastatic RCC (mRCC), including local therapies and systemic therapies.[3] The discussion that follows outlines our approach to local and systemic therapies in patients who have mRCC with brain metastases.

Brain metastases in mRCC are usually small and asymptomatic when found on screening (ie, routine staging before clinical trial enrollment or standard-of-care systemic therapy). However, brain metastases can present symptomatically and be quite large, which is of course a very different scenario. RCC metastasizes less often to the brain than to other sites. For example, a review of the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) found that among 2027 patients with mRCC, the incidence of metastasis to the brain was 8%, compared with 69% to the lungs, 43% to the lymph nodes, 34% to the bones, and 19% to the liver.[2] In other large series, including a population-based analysis conducted in Italy (n=11,157) and a global expanded-access study of sunitinib (Sutent, Pfizer; n=4543), the incidence of metastasis to the brain ranged from 7% to 8%.[4,5] Moreover, particular sites of metastatic disease were associated with a greater likelihood of brain metastasis. The rate of brain metastasis was 2% in patients with abdominal metastases only vs 16% in patients with thoracic and bone metastases.[4]

Brain metastases in patients with mRCC negatively affect the prognosis. In a retrospective cohort of patients with mRCC treated for brain metastases between 1975 and 1993 at Institut Gustave Roussy, Villejuif, France, the median survival time after a diagnosis of brain metastasis was 7 months.[6] In a more contemporary series of patients treated at the University of California, Los Angeles, between 1989 and 2006, the median overall survival time after a diagnosis of brain metastasis was 10.7 months, with survival rates of 48% at 1 year, 30% at 2 years, and 12% at 5 years.[7] In the era of targeted therapy, according to the IMDC (2005-2011), the median survival time after first-line treatment with targeted therapy was 14.4 months for patients with brain

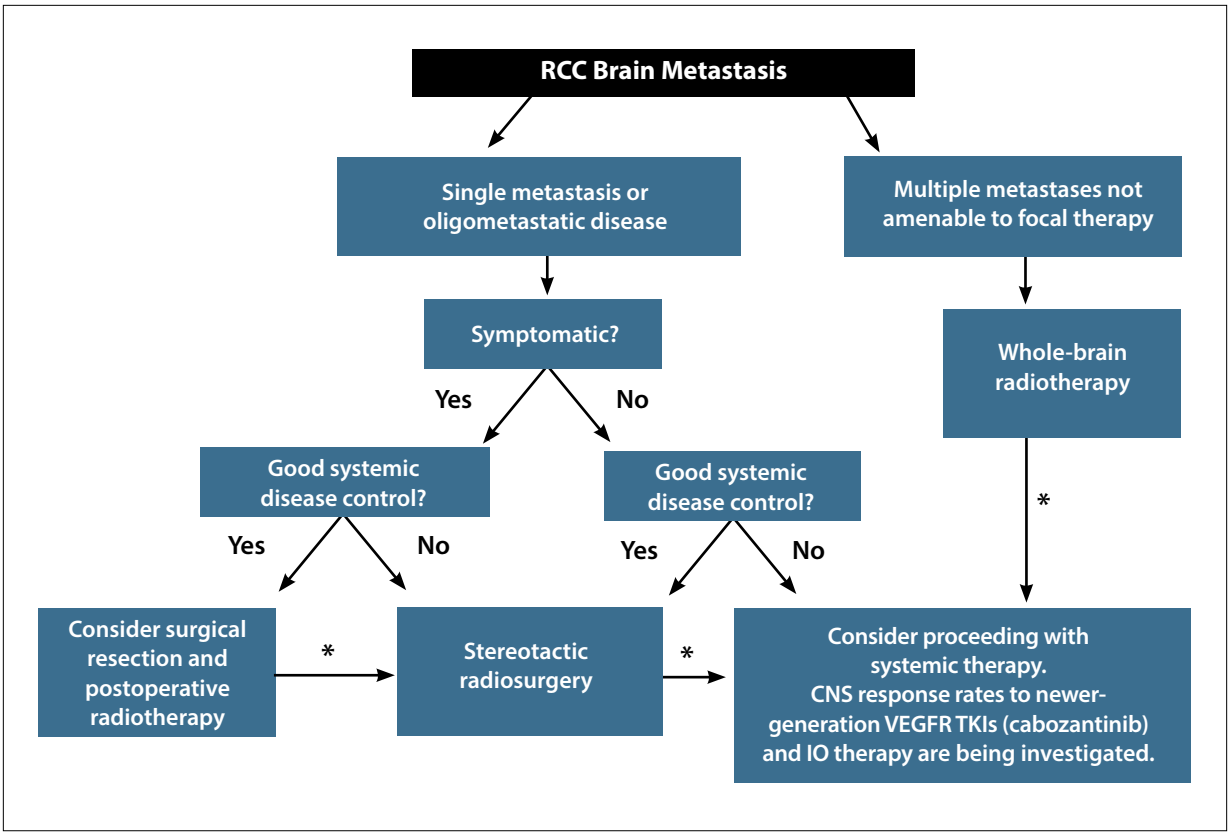

Figure. Algorithm for treatment of brain metastasis in patients with renal cell carcinoma.

* CNS recurrence.

RCC, renal cell carcinoma; SRS, stereotactic radiosurgery; VEGFR, vascular endothelial growth factor receptor; TKI, tyrosine kinase inhibitor; IO, immuno-oncology (e.g. checkpoint inhibitors like nivolumab); CNS, central nervous system.

metastasis vs 19.0 months for those with no brain metastasis.[8] On multivariate analysis, a Karnofsky performance status of less than 80, a time from diagnosis to treatment with targeted therapy of less than 1 year, and a higher number of brain metastases (>4) were associated with worse survival after a diagnosis of brain metastases.

Local Therapy

Local therapy is effective for brain metastasis in mRCC. The main modalities of local therapy are surgical resection, stereotactic radiosurgery (SRS), and whole-brain radiotherapy (WBRT), alone or in combination (see Figure). The number of metastatic lesions within the brain, the site(s) of the lesion(s) (accessible vs not accessible), the size of the lesion(s), the symptoms, the status of extracranial disease, and the available local expertise may determine treatment options. Surgical resection is a standard of care for patients who have a solitary brain metastasis in an accessible location and well-controlled extracranial disease. SRS is typically used for limited-volume brain metastasis and WBRT for more widespread brain metastasis. We find that what constitutes "limited volume" depends on the experience of the radiation oncologist; however, it typically means 5 to 10 lesions or fewer. A large study of patients with multiple brain metastases (n=1194), of whom 3% (n=36) had mRCC, suggested that SRS is safe and effective for those with up to 10 brain metastases.[9]

Thus, SRS has become our treatment of choice for the vast majority of patients who have mRCC with brain metastasis. We find that relatively few patients are good candidates for surgical resection (although it should still be strongly considered), and WBRT is typically not very effective. In one retrospective study of WBRT in patients who had mRCC with brain metastasis, median survival was 4.4 months.[10] SRS series have shown very good local control and, although there is certainly selection bias in the literature, relatively good survival as well. For example, a retrospective series by Wowra and colleagues (n=75,350 lesions treated) demonstrated a 95% actuarial rate of local tumor control after initial gamma knife surgery, with a

median survival of 11.1 months.[11] There is evidence that with SRS, *extracranial* tumor control is improved with a single high dose vs a hypofractionated regimen.[12] This seems also to hold true for *intracranial* disease; compared with a dose of 16 to 18 Gy, SRS with 20 Gy demonstrated better local control (12-month local control rates of 50% and 81%, respectively; *P*=.001). In some cases, the combination of SRS with surgery may be appropriate. A consecutive series of SRS alone, surgery plus SRS, and WBRT plus SRS demonstrated overall survival times of 13.9 months, 21.9 months, and 5.9 months, respectively, with local control rates of 84%, 94%, and 88%.[13] However, WBRT should probably be added to SRS only in patients with multiple metastases and a poor prognosis.[14] Although little evidence specific to brain metastasis in mRCC is available, across tumor types it appears that local control with SRS decreases as the size of the lesion increases, with a threshold of 2 cm before the risks for both recurrence and radionecrosis or CNS toxicity increases (both also depending on dose, which must be decreased as volume increases).[15-18] Lesions greater than 4 cm are generally considered too large for SRS. In summary, although mRCC generally has been considered radioresistant, this may not be the case.[19] High-dose, single-fraction SRS should be considered for patients who are not candidates for surgical resection, depending on the number of brain metastases and the prognosis.

Medical Treatment

Cytotoxic systemic therapies traditionally are not used to treat brain metastasis in patients with cancer, given that the brain is thought be a sanctuary site protected by the impermeable blood-brain barrier.[20] The blood-brain barrier consists primarily of specialized tight junctions between cerebral capillary endothelial cells, surrounded by a matrix of basal lamina, astrocyte end-feet, microglia, and pericytes. These form a tightly regulated niche that allows only the passive diffusion of small lipophilic molecules such as essential gases (ie, oxygen, carbon dioxide) and the active transport of essential nutrients.[21] Depending on the tumor type, however, the blood-brain barrier may break down to some degree in patients with brain metastases, allowing drugs that are water-soluble but normally do not reach the brain to reach tumors in variable concentrations.[22,23] During the last decade, the US Food and Drug Administration (FDA) has approved 10 systemic therapies for the treatment of mRCC, including agents targeting the vascular endothelial growth factor receptor (VEGFR) and mammalian target of rapamycin (mTOR), as well as immune checkpoint inhibitors. To date, several studies have examined the efficacy of these targeted therapies.

VEGFR tyrosine kinase inhibitors (TKIs) that are FDA-approved for the treatment of mRCC include sunitinib, pazopanib (Votrient, Novartis), sorafenib (Nexavar, Bayer), axitinib (Inlyta, Pfizer), cabozantinib (Cabometyx, Exelixis), and lenvatinib (Lenvima, Eisai; approved in combination with everolimus [Afinitor, Novartis]). Cabozantinib may be unique in that it additionally inhibits MET and AXL, and both cabozantinib and lenvatinib may inhibit fibroblast growth factor receptors (FGFRs) 1 through 4. The central nervous system (CNS) activity of the VEGFR TKIs that were initially approved has not been promising to date. Sunitinib has long been a standard of care as first-line therapy for patients with metastatic clear cell RCC. Only one prospective study, a phase 2 trial of sunitinib in patients with untreated brain metastases, has examined the CNS efficacy of VEGFR TKIs in patients with mRCC.[24] Among 16 evaluable patients, the CNS response rate was 0%, and the percentage of patients with stable disease was 31% (5/16). The median time to progression was 2.3 months, and the median overall survival was 6.3 months. CNS toxicities were limited, with no neurologic adverse events attributable to sunitinib, but the overall efficacy was not significant. Thus, sunitinib does not appear to have clinically significant activity in patients who have mRCC with brain metastasis.

The potential efficacy of other targeted therapies and immuno-oncology approaches is still being explored, and one recent study is the largest to date in terms of the molecular characterization of brain metastatic tissue in patients with mRCC. This study reported the intratumoral heterogeneity of MET and programmed death ligand 1 (PD-L1) expression in primary tumors vs metastatic biopsy tissues in patients with mRCC.[25] Of 180 resected RCC specimens examined, 87 specimens included brain metastases, 51 included pancreatic metastases, and 42 were primary specimens. Immunohistochemical staining indicated rates of PD-L1 expression in primary tumors, brain metastases, and pancreatic metastases of 12%, 23%, and 19%, respectively. Rates of PD-L1 expression in immune cells from the same sites were 50%, 47%, and 49%, respectively. The rate of MET expression was 0% in primary tumors and 2% in pancreatic metastases, but as high as 35% in brain metastases. Rates of discordance between primary tumors and brain metastases in terms of PD-L1 expression in tumor cells, PD-L1 expression in immune cells, and MET expression were 40%, 22%, and 67%, respectively. This analysis of brain metastases in mRCC provides a biological rationale to suggest that more recently FDA-approved systemic therapies targeting MET and PD-L1 may have therapeutic potential for patients with brain metastasis.

Cabozantinib is a VEGFR TKI with additional activity against c-MET, AXL, and RET. Cabozantinib

was first approved by the FDA as a second-line systemic therapy in mRCC on the basis of results of the phase 3 METEOR study (A Study of Cabozantinib vs Everolimus in Subjects With Metastatic Renal Cell Carcinoma), in which 658 patients whose disease had progressed after VEGF-targeted therapy randomly received either 60 mg of cabozantinib daily or 10 mg of everolimus daily.[26] Progression-free survival was 7.4 months with cabozantinib and 3.8 months with everolimus, and updated median survival data were significantly better with cabozantinib than with everolimus (21.4 vs 16.5 months).[27] Of note, although patients with known brain metastases who had been treated and had stable disease were eligible for the study, only 2 such patients were enrolled in the cabozantinib arm (2/330). Cabozantinib has also now received first-line approval in mRCC based on the phase 2 CABOSUN study (Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk), in which patients with intermediate- to high-risk disease had better median progression-free survival with cabozantinib than with sunitinib (8.2 vs 5.6 months).[28] Although cabozantinib has demonstrated significant systemic activity, the CNS response rate in patients with mRCC still requires exploration. As detailed previously, MET expression is present in a significant proportion of brain metastases from mRCC. Preclinical studies show that cabozantinib does achieve CNS penetration in whole-brain lysates of non–tumor-bearing mice. Cabozantinib has also been shown to induce tumor response in metastatic non–small cell lung cancer, as well as in glioblastoma.[29-31] Anecdotally, we have observed cabozantinib-induced responses in patients who have mRCC with brain metastasis. Cabozantinib could be an option for patients with progression after local therapy, or for those who are not candidates for local therapy. Of note, the phase 2 study that led to the FDA approval of lenvatinib in combination with everolimus for the treatment of mRCC did exclude patients with brain metastasis, and clinical data are lacking regarding the CNS efficacy of this combination.[32]

Immuno-oncology approaches to the treatment of brain metastasis are also of growing interest. Although the permeability of monoclonal antibody checkpoint inhibitors across the blood-brain barrier is likely variable, these therapies work by boosting the function of T cells, which likely traffic across the barrier.[33] Furthermore, evidence exists suggesting that brain metastases exist in an inflammatory microenvironment, which may harbor significant quantities of tumor-infiltrating lymphocytes, making checkpoint inhibitors a plausible therapeutic strategy.[34] Several retrospective series have indicated that immune checkpoint inhibitors may achieve a response in treating CNS disease in melanoma and non–small cell lung cancer,[33] and early results of a prospective phase 2 study of patients with previously untreated brain metastasis treated with the programmed death 1 (PD-1) inhibitor pembrolizumab (Keytruda, Merck) showed a 22% response rate in patients with melanoma (n=18) and a 33% response rate in patients with non–small cell lung cancer (n=18).[35]

As mentioned above, a significant proportion of brain metastases in mRCC (tumor cells), as well as immune cells in the microenvironment, are positive for PD-L1. Data from prospective trials of treatment in patients with mRCC are limited, but some early descriptions of patients treated with the PD-1 inhibitor nivolumab (Opdivo, Bristol-Myers Squibb) for mRCC have been reported. One analysis specifically looked at the response rates of patients with brain metastases in the NIVOREN trial (Nivolumab in Patients With Metastatic Renal Cell Carcinoma Who Have Progresses During or After Prior Systemic Anti-angiogenic Regimen), also called GETUG-AFU 26. NIVOREN was a phase 2 study examining the efficacy of nivolumab in the systemic therapy of mRCC after the failure of at least 1 or 2 previous systemic treatments.[36] Of the 588 patients enrolled, 55 had asymptomatic brain metastases, including 67%, 12%, and 21% with 1, 2, or more than 2 brain metastases, respectively. Of the 55 patients, 37 (67%) had had no previous treatment for brain metastases, 5 (9%) had undergone brain surgery, and 17 (31%) had undergone brain radiation. The median duration of therapy in the patients with brain metastases was 2.4 months (range, 0-9 months). Of 44 patients with brain metastases who were assessed for response, 10 (23%) had an objective response and 21 (48%) had progressive disease. Neurologic decline requiring corticosteroid treatment developed in 15 patients (34%). Although this study was small, it did show a potential response that requires further exploration. Prospective clinical trials, including approaches combining radiotherapy with immuno-oncology, are under way (NCT02978404). In our experience with patients who have mRCC with brain metastasis and are treated with immuno-oncology therapies, neurologic symptoms (eg, seizures) appear more likely to occur when the dose of prednisone has not been tapered to 10 mg daily (or the equivalent) or less and the patient has demonstrated stability on this dose.

Conclusion

We continue to search for more effective therapeutic options for patients who have mRCC with brain metastases. Surgery and radiation remain the main therapies for symptomatic patients, and the development of SRS has improved our ability to treat patients with a limited number of brain lesions. There is little proof of efficacy

for systemic therapies to date, but they may provide an option for patients in whom local therapy fails. Although VEGFR TKIs have had success in extracranial disease, CNS response rates have been modest. Anecdotal reports of cabozantinib CNS activity must be explored, and the clinical use of cabozantinib may be reasonable based on our experience. Brain metastases from other tumor types, most notably melanoma and non–small cell lung cancer, have shown responses to immune checkpoint inhibitors, and some preliminary data indicate CNS responses to immuno-oncology therapy in mRCC as well.

Disclosures

Dr Ramalingam has received institutional research funding from Exelixis. Dr George has consulted for or received institutional research funding from Acceleron, Acerta, Astellas/Medivation, AstraZeneca, Bayer, BioPharm, Bristol-Myers Squibb, Dendreon/Valeant, Exelixis, Genentech, Janssen, Merck, Millennium, Myovant Sciences, Novartis, Pfizer, Sanofi-Aventis, and Viamet/Innocrin. Dr Harrison has received institutional research funding from Argos, Bristol-Myers Squibb, Exelixis, Genentech, and Pfizer; has done consulting for Exelixis, Genentech, and Pfizer; and has served on the speaker's bureau for Exelixis and Genentech.

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