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The impact of tyrosine kinase inhibitors on the multi-modality treatment of brain metastases from renal cell carcinoma

Jonathan Verma, M.D.¹, Eric Jonasch, M.D.², Pamela K. Allen, Ph.D.³, Jeffrey Weinberg, M.D.⁴, Nizar Tannir, M.D.², Eric Chang, M.D.³, and Anita Mahajan, M.D.³

¹Department of Radiation Oncology, The Methodist Hospital, Houston, TX

²Department of Genitourinary Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

³Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

⁴Department of Neurosurgery, The University of Texas MD Anderson Cancer Center, Houston, TX

Abstract

Objectives—This study evaluated the effect of tyrosine kinase inhibitors (TKI's) on the brain metastasis (BM) local control (LC) and overall survival (OS) of patients with renal cell carcinoma (RCC) with BM.

Methods—A retrospective review of patients with RCC BM was conducted. Eligible patients from two eras: pre-TKI, 2002–2003, and post-TKI, 2006–2007, were identified. Prognostic factors, use and type of systemic therapy were noted. The timing, number, size, and treatment modality data for each BM was recorded. Use of TKI and BM treatment modality were correlated to LC and OS.

Results—Eighty-one patients with 216 brain metastases were identified. 37 patients had BM at diagnosis and 44 were found to have BM later. 41 patients never received a TKI and 40 patients received TKI's. Stereotactic radiosurgery (SRS), surgery, whole brain radiotherapy (WBRT), or no local brain treatment was used for 89, 19, 24, and 75 lesions, respectively. The median OS from BM diagnosis was 5.4 months for the whole group: 4.4 months versus 6.71 months in the never-TKI versus TKI groups, respectively. Patients who received TKI's post-BM development had a median OS of 23.6 months vs. 2.08 and 4.41 months for the patients who received TKI's pre-BM or never-TKI, respectively, ($p=0.0001$). Local control was statistically superior in lesions managed with surgery or SRS vs. the no local therapy.

Send correspondence to: Anita Mahajan, MD, Department of Radiation Oncology, M.D. Anderson Cancer Center, Box 097, Houston, TX 77030, amahajan@mdanderson.org.

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Conclusions—In patients with RCC and BM, TKI's are associated with a trend to improved OS, but no significant improvement in LC of BM. They may provide a significant benefit to patients with BM with no prior TKI exposure.

Introduction

The advent of antiangiogenic agents, specifically the orally bioavailable receptor tyrosine kinase inhibitors (TKIs) has had a dramatic impact in the management of patients with metastatic renal cell carcinoma (RCC). These agents provide variable inhibition of kinases in several intracellular pathways including the vascular endothelial growth factor (VEGF) pathway that is thought to play a key role in the pathogenesis of RCC[1–3]. Within the last 5 years, several TKI agents, including sunitinib, sorafenib, and pazopanib, have been approved and are now in wide use in mRCC the first-line and cytokine-refractory settings.

Brain metastasis (BM) occurs in approximately 8–11% [4] of the over 58,000 patients diagnosed annually[5] with RCC. There is early evidence that TKIs may have activity in the brain Retrospective analysis of the phase III trial randomizing patients between sorafenib and placebo found lower crude rates of BM in the group receiving the drug[6]. Our own retrospective data from the MD Anderson Cancer Center (MDACC) found sunitinib and sorafenib to be protective with regard to BM development[7]. Finally, there are case reports describing BM response to systemic therapy with a TKI agent in the absence of any local therapy[8, 9]. However, the literature evaluating the impact of these agents on outcomes in patients with existing BM is limited. Vogl et al reported limited benefit of targeted therapy in patients with RCC-BM, but the study included only 12 patients with BM, and neither OS nor PFS was statistically affected [10]. The purpose of our study is to evaluate the impact of TKIs, in conjunction with local therapies such as surgery or types of radiation therapy (external beam vs. radiosurgery), on outcomes in patients with RCC and BM, including rates of local control (LC), overall survival (OS), and distant brain metastasis-free survival (DBMFS).

Materials / Methods

Patient selection

We retrospectively searched the MDACC tumor registry database for patients who presented to the institution with stage IV clear cell RCC between 2002–2003 and 2006–2007, and either had BM at diagnosis or developed BM at any point during clinical follow-up. Given the introduction of sunitinib and sorafenib in early 2006, we expected that choosing these dates would create a control group of patients who were TKI naïve to which we could compare those who received TKIs. We considered any patient who was treated with TKIs in the TKI treatment group regardless of the year in which they were diagnosed. We excluded patients who had sarcomatoid, papillary, or chromophobe features on histological examination, and those who never developed BM. This study was approved by our institutional review board.

Data review

The following data were extracted from the medical records for review: age, gender, ethnic group, Fuhrman nuclear grade, involved sites of metastatic disease at diagnosis (including brain, liver, adrenal glands, lung, bone, and retroperitoneal and mediastinal lymph nodes); whether the patient had undergone nephrectomy; Memorial Sloan Kettering Cancer Center (MSKCC) risk category[11], a widely accepted risk stratification method calculated using serum lactate dehydrogenase, hemoglobin, corrected serum calcium, performance status, and time from diagnosis to systemic therapy; treatment with the TKIs sunitinib or sorafenib or other systemic agents; number and location of BM, treatment modality for BM (surgery, external beam, radiosurgery), and location and treatment of brain recurrence; vital status; and duration of follow-up. For the purposes of evaluating LC, each individual metastasis was considered a unique data point.

We considered patients to have received TKIs if they received one of either sunitinib or sorafenib at any point. In our analysis, we further subdivided the TKI group based on the timing of their TKI treatment relative to the diagnosis of BM, considering patients whose progression to BM occurred while on TKI (“Progression”) and those whose first exposure to TKI was after they had existing BM (“Naive”). We compared these patients to the group who never received TKIs at any point in their treatment (“never-TKI”).

Statistical analysis

The frequencies of all clinical and pathological features were compared by using the Chi-square statistic. Continuous variables were compared using Student’s *t* test. OS, LC, and DBMFS were estimated by using the Kaplan-Meier method. All statistical analysis was performed using Stata/MP 11.1 for Windows[12].

Results

Our search identified 81 eligible patients (Table 1) with a total of 216 unique brain metastases. Thirty-seven (46%) patients had BM at diagnosis of RCC, and the remaining 44 (54%) were diagnosed with BM at a later point during their clinical follow-up. The median age at diagnosis of BM was 59 years (range, 40.2–80.6 years). Median follow-up time from BM for all patients was 5.4 months (range, 0.13–78 months). Data for each group is presented in Table 1. There was no significant difference in patient characteristics for each group.

Forty-one patients (50.6%) never received a TKI agent, and the remaining 40 patients (49.4%) were treated with TKIs. We found no significant differences between the groups with regard to age, sex, nuclear grade, sites of distant metastases at diagnosis, or MSKCC risk category (Table 1). As we expected for patients treated over different time periods, the systemic agents did differ between the two groups. Specifically, more patients in the era before TKIs became available (i.e. the never-TKI group) were treated with agents such as interferon, interleukin-2, 5-fluorouracil, and gemcitabine. A higher number of patients in the TKI group were also treated with bevacizumab, erlotinib, and temsirolimus.

The 81 patients had a total of 216 individual brain metastases. Data for these BM, organized by local treatment modality, is presented in Table 2. Of these, 153 (71%) were present at the initial diagnosis of BM, and the remaining 63 (29%) represented distant CNS recurrence in a patient previously diagnosed with BM. At initial diagnosis of BM, 47 patients (58%) had a solitary BM, 18 (22%) had 2 or 3 BM, and 16 (20%) had greater than 3 metastases. There was no significant difference in numbers of BM between TKI and never-TKI groups (Table 2).

The first single local treatment for individual metastases consisted of: SRS for 89 lesions, surgical resection for 19 lesions, WBRT for 24 lesions, and no local therapy for 75 lesions (Table 2). The remaining lesions were treated with different therapy combinations, such as SRS or surgery followed by WBRT. Data for these lesions were not included in our analysis of local therapy.

The median survival from BM diagnosis to last follow-up date for all patients was 5.4 months (0.20–78 months). Median survival in the never-TKI group was 4.41 months (0.20–39 months) versus 6.71 months (0.29–78 months) in the TKI group ($p=0.07$). We also analyzed OS by separating patients into groups based on the timing of their TKI treatment relative to BM development. The naïve group, ie, those patients who first received a TKI agent after BM development, had a median survival of 23.6 months (1.8–78 months), which was significantly longer than median OS in the Progression and never-TKI groups at 2.08 months (0.29–14 months) and 4.41 months, respectively ($p=0.0001$). OS is presented in Figure 1.

We analyzed LC for individual metastases based on the type of local treatment received (Figure 2). LC rates at 1 year for specific BM treated with surgical resection and SRS were 83.6% and 75.6% respectively ($p=0.55$). At 1 year, the actuarial LC rate for lesions treated with WBRT and observation only were 53.3% and 36.4% respectively. Both surgical resection ($p=0.002$) and SRS ($p<0.0001$) were superior to observation without local treatment. The difference in local control between surgical resection or SRS and WBRT did not reach statistical significance ($p=0.15$, $p=0.18$ respectively).

We also examined LC as a function of TKI treatment status. One-year actuarial rates of LC in the TKI and non-TKI groups were 69% and 55% respectively ($p=0.051$). However, it should be noted that this comparison does not account for different local therapies that were utilized in the treatment of these metastases. A higher percentage of tumors in patients treated with TKIs were treated with SRS, while a higher proportion of tumors in the never-TKI group were observed without local therapy (Table 2). In the subgroup of tumors treated with SRS, we found 6-month and 1-year rates of LC of 94.7% and 75% in the group treated with TKIs, and 73.7% in the group that did not receive the drugs ($p=0.09$). Further analysis of this subgroup based on the timing of their TKI treatment revealed that the naïve, progression, and no-TKI groups had 1-year LC rates of 90%, 53%, and 74%, respectively ($p=0.18$) (Figure 3). LC in the naïve group was not found to be statistically superior to that in the no-TKI group ($p=0.12$). Similarly, we did not observe a statistically significant enhancement of LC in the subgroups of patients treated with surgical resection or observation without local therapy (Figure 3). We also found no differences in 1-year

actuarial rates of DBMFS between the naïve, progression, and no-TKI groups, at 43.2%, 0%, and 49%, respectively ($p=0.39$) (Figure 4).

Four patients who underwent SRS developed radionecrosis at a treated site. These patients were treated with a dose of 18–20 Gy to their BM. One patient required resection of the necrotic area, and pathologic review confirmed the presence of necrotic tissue with no viable tumor cells. The patients were evenly split by TKI status, with 2 in the TKI group and 2 in the non-TKI group.

Discussion

In this study, we sought to examine the effect, if any, of TKI systemic therapy in the management of BM from RCC. Our findings suggest that these agents may provide a survival benefit in patients with BM, and particularly so in the subgroup of patients with BM who are TKI-naïve. However, we did not observe any statistically significant improvement either in rates of LC or DBMFS in our patient population. Taking our findings together, we conclude that these agents have only a marginal benefit in the management of BM from RCC, and any survival benefit we observed is likely due to improved control of systemic disease.

Patients with BM generally have a poor prognosis. Previous studies have found a median length of survival of between 3 and 5 months after BM development[13–15]. Our findings are consistent with those in the literature, with a median survival time of 5.4 months in all patients. We found that patients treated with TKIs had a trend towards a survival advantage when compared to their non-TKI treated counterparts. However, the improved survival we observed, 6.71 months versus 4.41 months, indicates that BM remains a poor prognostic factor in the era of targeted therapies. The subset of patients who were TKI-naïve at the time of BM development did, however, have a significantly improved median survival compared to all other groups. We speculate that the underlying tumor biology in these patients differs from that of patients who progressed to BM on TKIs, making the former group more responsive to the effects of the drugs. However, given that these patients did not have any improvement in rates of new CNS metastasis, it is likely that the survival benefit can be attributed to improved control of systemic rather than CNS disease.

The results of our study also reaffirm the need for local therapy with surgery or radiotherapy to successfully locally control BM. Previous studies have shown SRS to provide LC rates for BM as high as 96% [16–18]. WBRT, on the other hand, is less able to provide LC for these tumors. Wronski et al, in their review of 119 patients treated with WBRT, found median survival of only 3 months, with neurologic causes the most common cause of death [15]. Halperin and Harisiadis reported neurologic symptom improvement in only 30% of patients treated with WBRT [19]. In our population, we found no difference in LC rates between individual metastases treated with SRS and surgery. Of course, clinical factors guided treatment selection for metastases in this retrospective study, making it difficult to directly compare treatments. For instance, metastases that were selected for surgical resection were significantly larger than those treated with radiotherapy. There may also have been differences in peritumoral edema, treatment with steroids, performance status, or other

clinical variables. However, we can conclude that SRS and surgery can provide high rates of LC for BM in appropriately selected patients. In addition, we believe both modalities are superior at achieving LC than WBRT or systemic therapy alone.

In our population, we did not find TKIs to provide a statistically significant enhancement to LC rates obtainable with local therapy with surgery or radiotherapy. Patients receiving SRS and TKIs had 6-month LC rates of 94.7%, versus 73.7% in the group who received SRS without TKIs. The difference was not statistically significant ($p=0.09$), but it gives us pause in concluding that the agents offer no benefit to LC. It is possible that sample size, inconsistency in duration of TKI treatment, or patient selection factors limit our ability to detect a statistically significant difference. Another topic of great interest is whether TKIs exacerbate toxicity of treatment. Four patients who received SRS did develop radiation necrosis, and one case required surgical resection. Two of these patients received TKIs, and 2 did not. The small number makes it difficult to assess for variables that may have contributed to rates of toxicity, but it is fair to say that the TKIs did not greatly increase the risk of radionecrosis. Our findings are consistent with those of Staehler et al, who recently reported no complications in 51 patients treated with SRS and simultaneous anti-angiogenic therapy[20]. Nonetheless, further research is needed to assess what role TKIs play in treatment of BM in addition to existing local therapies.

In our previous study, we found that patients treated with TKIs had lower rates of BM development when compared to those who did not receive TKIs [7]. However, contrary to our expectations, we did not find TKIs to be associated with any benefit in rates of new BM in patients with pre-existing BM. A possible explanation for this observation is in underlying tumor biology; it is possible that once a tumor has developed the ability to circumvent the TKIs effect and metastasize to the brain, the drugs are no longer able to protect from future BM. In our population, approximately 50% of patients with BM eventually developed a second CNS metastasis, highlighting the importance of regular screening for BM in this high-risk group. This study has some limitations, first among them its retrospective nature. It is difficult to compare outcomes in patients non-randomly selected, based on clinical criteria, to receive various local and systemic therapies. There may have been inconsistencies in the duration of TKI treatment. Finally, this retrospective study was limited to the available data, which may have been incomplete in some cases. Further research is warranted to study the outcomes and adverse effects of TKIs in the management of RCC and BM.

In conclusion, TKIs have a limited role in the management of BM from RCC. These agents are associated with a trend towards improved survival in patients with BM and a statistically significant improvement in survival in the subgroup of patients who are TKI-naïve at the time of BM development. However, in our analysis we did not detect an improvement in LC or DBMFS, suggesting that a large part of the survival advantage may be due to improved control of systemic disease rather than any effect on BM. Local therapy with SRS or surgical resection can achieve high rates of LC provided that these modalities are utilized in appropriately selected patients.

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Figure 1.

Overall survival of all patients by TKI status. Figure 1a illustrates the difference in survival with and without TKI. Figure 1b Illustrates the difference between patient who never received TKI in contrast to those who received TKI before (naïve) or after (progression) brain metastasis.

Figure 2.
Brain metastasis local control by the different local treatment modalities

Figure 3. Brain metastasis local control by TKI status with **a)** stereotactic radiosurgery, **b)** surgical resection and **c)** observation

Figure 4.
Distant brain metastasis-free survival according the TKI status.

Table 1

Patient Characteristics

Variable	All (n=81)	Never-TKI (n=41)	TKI (n=40)	P
Median age at BM diagnosis (y)	59	58.6	59.2	0.66
Sex (%)				
Male	50 (62)	26 (63)	24 (60)	0.75
Female	31 (38)	15 (37)	16 (40)	
Fuhrman grade (%)				0.17
2	12 (15)	4 (9.7)	8 (20)	
3	30 (37)	12 (29)	18 (45)	
4	17 (21)	11 (27)	6 (15)	
Unavailable	22 (27)	14 (34)	8 (20)	
Distant Mets at Diagnosis				
Adrenal Glands	13 (16)	7 (17)	6 (15)	0.79
Brain	37 (46)	18 (44)	19 (48)	0.75
Bone	20 (25)	10 (24)	10 (25)	0.95
Liver	9 (11)	5 (12)	4 (10)	0.75
Lung	71 (88)	35 (85)	36 (90)	0.53
Mediastinal Nodes	27 (33)	14 (34)	13 (32)	0.87
Number of BM at diagnosis of BM (%)				0.47
1	47 (58)	26 (63)	21 (52.5)	
2–3	18 (22)	9 (22)	9 (22.5)	
>3	16 (20)	6 (15)	10 (25)	
MSKCC risk category				0.33
Low (0)	25 (31)	15 (37)	10 (25)	
Intermediate (1–2)	48 (59)	21 (51)	27 (67.5)	
High (2+)	8 (10)	5 (12)	3 (7.5)	

Table 2**Metastases**

Variable	SRS (n=89)	Surgery (n=19)	WBRT (n=24)	Observation (n=75)	P
No. of patients	34	16	13	33	
Mean BM per patient (range)	2.6 (1–19)	1.2 (1–2)	1.9 (1–5)	2.3 (1–9)	0.27
Median size (range), cm	0.5 (0.2–2.3)	2.7 (0.3–7.1)	0.8 (0.3–3.0)	0.5 (0.2–2.1)	<0.001
TKI status					<0.001
Never-TKI (n=81)	25 (31)	9 (11)	10 (12)	37 (47)	
TKI (n=126)	64 (51)	10 (7.9)	14 (11)	38 (30)	
Naïve (n=48)	23 (49)	9 (19)	1 (2)	15 (32)	
Progression (n=78)	41 (53)	1 (1.3)	13 (17)	23 (29)	