Response to radiation in renal medullary carcinoma

Alexandra M. Walsh,[1] John B. Fiveash,[2] Alyssa T. Reddy,[1] Gregory K. Friedman[1]

[1]Division of Pediatric Hematology Oncology, University of Alabama at Birmingham, Birmingham, AL; [2]Department of Radiation Oncology, University of Alabama at Birmingham, Birmingham, AL, USA

Abstract

Renal medullary carcinoma (RMC) is a rare and highly aggressive malignancy arising from the renal medulla and found mostly in patients with sickle cell trait. RMC usually presents with widely metastatic disease. We describe a young man diagnosed with metastatic RMC who sustained a complete response to systemic chemotherapy but developed brain metastases with leptomeningeal involvement and subsequently had a partial response to brain irradiation. The use of radiation in the management of RMC is reviewed. Due to the apparent propensity for RMC to spread to the central nervous system, prophylactic treatment such as craniospinal irradiation should be considered along with chemotherapy in patients with metastatic RMC to potentially improve the progression-free interval.

Introduction

Renal medullary carcinoma (RMC) is an aggressive malignancy seen primarily in young African-American patients with sickle cell trait. We report the case of an 11 year old with metastatic RMC without central nervous system (CNS) involvement at diagnosis who developed brain metastases with evidence of leptomeningeal spread 11 months after having a complete response (CR) to 9 cycles of multi-agent chemotherapy. Brain radiation provided the patient with palliation, and his brain metastases shrank as a result of the radiation. The use of radiation in the management of RMC is reviewed, and based on the likely propensity for RMC to spread to the CNS, the use of CNS prophylactic therapy such as craniospinal irradiation (CSI) should be considered in patients with metastatic RMC.

Case Report

An 11 year old African-American male without medical problems but a known diagnosis of sickle-cell trait initially presented with back pain and cough as well as weight loss and neck swelling. A computed tomography (CT) scan showed a large left kidney mass, measuring 7.8×5.6×5.8 cm, wide-spread lymphadenopathy, bilateral pleural effusions and too numerous to count liver and lung nodules. A bone scan showed widespread bone metastatic disease. Of note, a brain CT scan was negative for disease. A biopsy confirmed RMC. He began treatment with paclitaxel, gemcitabine and carboplatin (PGC). The patient's tumor responded in all sites, and after three cycles of chemotherapy, he had a left nephrectomy, retroperitoneal lymph node dissection, and thoracoscopic removal of the pulmonary nodules.[1] Pathologic examination of all removed tissue showed no evidence of tumor, and radiologic evaluation was negative for disease. The patient underwent an additional six cycles (nine total) of combination chemotherapy. He remained disease-free for 11 months off therapy before presenting with persistent headaches, left leg weakness and hyperreflexia. A CT scan showed a right parietal abnormality and leptomeningeal enhancement. He was given IV dexamethasone, admitted to the hospital and underwent a magnetic resonance imaging (MRI) which showed 3 masses in the right parietal lobe with surrounding peripheral edema arising from the interhemispheric fissure (Figure 1 A-B). A CT scan of the chest/abdomen/pelvis and spinal MRI were negative for disease suggesting his relapsed was only in the CNS. The patient started radiation therapy as well as temozolomide orally at 75 mg/m^2 daily. Initially, he began 5 fractions (250cGy each) of whole brain radiation via a helmet field down to C2. Then, he began 10 fractions with an integrated boost plan to treat the remainder of the brain parenchyma, and he was given an additional 200 cGy x 10 doses with the gross tumor receiving 300 cGy in 10 fractions. In total, the patient received 3250 cGy in 15 fractions to the whole brain, and 4250 cGy in 15 fractions to the gross tumor. He tolerated the radiation well with only mild nausea during the second week of therapy. The patient had improvement in his weakness and headaches, and his dexamethasone was successfully weaned off one week after completing treatment. A repeat MRI one month after completing radiation showed decrease in the size of the lesions and significantly decreased edema (Figure 1C-D). One month later, the patient presented with worsening headache and malignant cells in the cerebrospinal fluid were confirmed via lumbar puncture. The patient was discharged into the care of hospice and died at home 1.5 months later.

Correspondence: Gregory K. Friedman, Department of Pediatrics, 1600 7th Ave South, ACC 512, Birmingham, AL 35233-1711, USA.
Tel. +1.205.939.9285 - Fax: +1.205.975.1941
E-mail: gfriedman@peds.uab.edu

Key words: renal medullary carcinoma, radiation, response, review.

Conflict of interest: the authors report no conflicts of interest.

Received for publication: 28 June 2011.
Revision received: 11 July 2011.
Accepted for publication: 13 July 2011.

Rare Tumors 2011; 3:e32
doi:10.4081/rt.2011.e32

Discussion

RMC is a rare and clinically aggressive tumor first described in 1997 and thought to arise from the renal collecting duct. RMC most commonly occurs in patients with sickle-cell trait.[2] There have now been three reports of long-term survivors of RMC who presented with localized tumors and underwent a complete resection.[3-5] However, most patients present with metastatic disease, and have traditionally had a very poor prognosis. The most common sites of metastatic disease at diagnosis include lung, retroperitoneal or mediastinal lymph nodes, bone and liver. There have also been several cases that initially presented with metastatic brain or spinal-cord lesions.[6-8] In one review of 64 patients with metastatic renal cell carcinoma other than the clear-cell type (including RMC, papillary, chromophobe and unclassified), only 2 patients (3%) presented with metastatic brain lesions. In contrast, 28 patients (41%) had lung and 30 (47%) had retroperitoneal lymph node disease at diagnosis.[9] Fifty-eight of 61 patients with RMC had metastases present at the time of diagnosis.[10] Although brain metastases at presentation in patients with RMC are uncommon, a brain MRI at the time of diagnoses would rule out occult metastases.

Initial reports of RMC revealed a median survival of 14 weeks after diagnosis.[2,5,11] However, there have been several recent reports that the combination chemotherapy regimen of PGC or cisplatin is active in patients with RMC and may prolong survival.[1,6,12,13] In addition to our patient who had a CR to PGC, a subsequent patient at our institu-

tion with RMC has had a CR with this same chemotherapy regimen.

There are now three reports in the literature of patients (including the report presented in this paper) who responded well to systemic chemotherapy outside of the CNS but developed or had worsening CNS disease.[1,6,12] Strouse *et al.* reported a case of a 17-year old African-American male with a right kidney RMC and multiple sites of bony metastatic disease at presentation. He underwent initial treatment with carboplatin alone and had significant improvement in the size of his tumors. After 27 weeks of therapy, the patient developed neck pain and headache. An MRI showed multiple brain lesions consistent with metastatic disease. Further workup showed no evidence of disease outside the CNS. The patient received palliative external beam radiation to the brain (3750 cGy) and thoracic spine (3000 cGy) while continuing the carboplatin therapy. Two months after completion of the radiotherapy, he had worsening back pain and evidence of progression of the brain and spinal metastases.[12] Our patient, similar to this patient developed recurrent disease in the CNS after treatment with a carboplatin-based regimen.

Schaeffer *et al.* described a case of a 35-year old African-American man with sickle-cell trait that developed a right kidney RMC and multiple metastatic lesions in mediastinal lymph nodes, lung and brain as well as an intracardiac mass. The patient underwent seven cycles of PGC with initial reduction in the size of the brain and lung lesions. After 6 months of therapy, the patient complained of headache and a repeat MRI showed an increase in size of the brain metastasis. The patient underwent palliative brain irradiation and started a salvage chemotherapy regimen with adriamycin and gemcitabine with an initial excellent response that lasted 9 months. The patient eventually relapsed in the lung and mediastinum and died 25 months after his initial diagnosis.[6]

Limited information has been published about the use of radiation for the treatment of RMC. Table 1 reviews the use of radiation in RMC in the published literature. Most investigators have used radiation for palliative pain control in metastatic sites, although Karaman *et al.* and Stahlschmidt *et al.* report the use of abdominal radiation as an adjunct to surgical resection and chemotherapy with little success.[14,15] Reports of palliative radiation for bone metastases have described a reduction in pain and some decrease in the size of lesions.[10,13,16] Avery *et al.* noted no response in pulmonary metastases to lung irradiation.[8] However, in addition to Strouse *et al.* and Schaeffer *et al.*, we noted a decreased size in brain metastases in our patient after brain irradiation (Figure 1).[6,12] Although the evidence is mixed, it appears that RMC is radiosensitive in many cases. There have been no reports of prophylactic CSI in RMC. For patients with residual CNS tumor after CNS fractionated radiation therapy, there may be a role for stereotactic radiosurgical boost, although there is no reported data on radiosurgery in this rare disease.

Upfront prophylaxis with either intrathecal chemotherapy or CSI in malignancies that tend to recur in the CNS may prevent the development of CNS disease. The routine use of CNS prophylaxis improved survival for childhood acute lymphoblastic leukemia dramatically.[17] Additionally, the use of prophylactic cranial irradiation in limited-stage small cell lung cancer has been shown to decrease the occurrence of CNS metastases, with a 5.4% survival advantage in those patients who had received irradiation (20.7% survival at 3 years in the treated group versus 15.3% in the control group).[18]

Based on our patient's impressive response to systemic therapy, and the fact that he never relapsed outside of the CNS, we speculate that the chemotherapeutic agents that he received may not have crossed the blood-brain barrier adequately to eradicate microscopic metastatic cells in the CNS that were likely present at diagnosis but not apparent on his initial

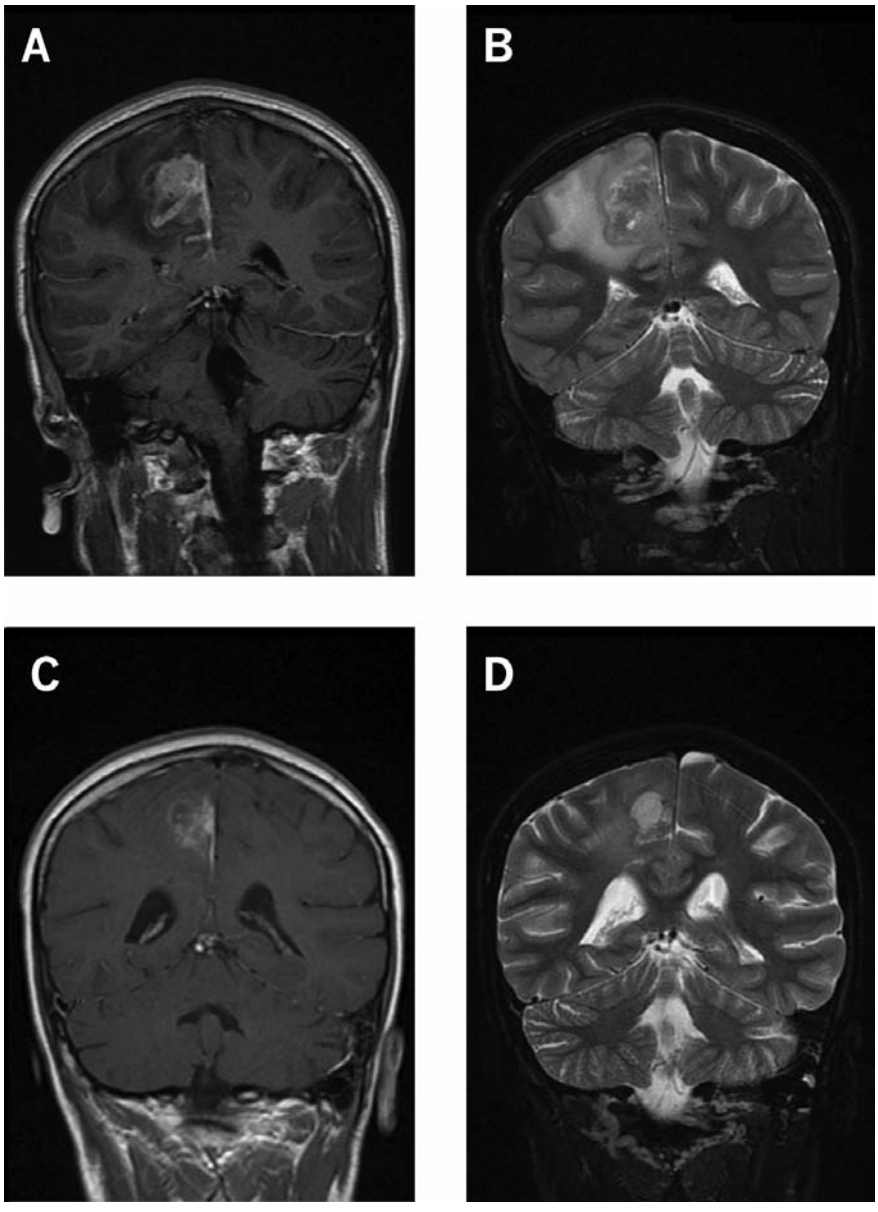

Figure 1. Magnetic resonance imaging of the brain, showing T1-post contrast (images on the left, A and C) as well as T2 flair images (images on the right, B and D). Images A and B demonstrate metastatic lesions in the right parietal lesion prior to radiation therapy. Images C and D were taken one month after radiation therapy and demonstrate an approximately 1/3 decrease in the size of the brain metastases as well as decrease in the surrounding brain edema.

Table 1. Summary of the available literature describing the use of radiation therapy for the treatment of renal medullary carcinoma.

Authors	Case	Chemotherapy regimen	Radiated location and dose (if known)	Response to radiation	Survival time, diagnosis to death
Schaeffer *et al.*[6]	35 yo male with gross hematuria, s/p laparoscopic RN, nodes +. 2 weeks post surgery developed mets to skin, mouth, lungs, brain, and heart. Enlargement of brain nodule post chemotherapy	Initial: 7 cycles carbo, GEM, paclitaxel Salvage: adria, GEM	Palliative to brain	Improvement in brain lesions	25 mo
Bell[13]	20 yo male with flank pain, fever, weight loss and large right kidney mass	10 cycles paclitaxel, GEM, cis	Palliative to bony mets	Improved pain control	10.5 mo
Avery *et al.*[8]	26 yo with right kidney mass with mets to lung, diaphragm and lymph nodes	α-interferon x 9 doses (no response)	Palliative to lung (3000 cGy)	No response	3 mo
Dimashkieh *et al*[19]	40 yo with lymphadenopathy, CT showed 2 masses in R kidney metastatic to supraclavicular LNs	Unknown	Unknown	Little benefit	5 mo
Karaman *et al.*[14]	7 yo right kidney mass, s/p RN, mets at diagnosis to LN, bones and lungs	VCN, actino-D, VP-16	Upfront 2160 cGy to operation region, 1080 cGy to tumor region as boost	Not good	4.5 mo
Simpson *et al*[10]	5 cases: 1. s/p RN 2. s/p RN 3. no RN 4. s/p RN 5. s/p RN	1. MVAC/Carbo/VP16 2. 5FU/GEM/ THAL, taxol/THAL 3. MVAC 4. MVAC,GEM/ docetaxel, VP16/ Carbo/ifos, Thal/capecitabine 5. Topotecan/adria	1. All tumor sites 2. Bone 3. Brain 4. Tumor sites 5. Lung	1. Complete (first line), partial (second line) 2. Mixed (response at existing sites with new mets) 3. Partial (first line) 4. Partial (first line), mixed (second line), progressive(salvage) 5. Progressive disease	1. 49 wks 2. 52 wks 3 63 wks 4. 64 wks 5. unk
Watanabe *et al.*[5]	19 yo with hematuria x 5 months, mets to lungs at diagnosis	GEM/cis	Unknown	Poor	5 mo
Rathmell *et al.*[16]	48 yo with gross hematuria, CT showed right kidney mass, s/p RN, mets to LNs and liver	Initial: sunitinib, no response Second-line: MVAC x 7 cycles	Palliative to painful bony met	Improvement in pain	Alive at time of publication
Strouse *et al.*[12]	17 yo with right RN. 3 months later presented with mets to lung, lymph nodes, bone and liver	Carbo	Palliative to brain (3750 cGy) and thoracic spine (3000 cGy)	Partial improvement	12 mo
Stahlschmidt *et al.*[15]	14 yo with sickle-cell disease presented with weight loss and abd pain. U/S showed mass in left kidney, RN, + paraaortic LNs	MVAC x 6 cycles	Upfront to abdominal sites of disease (4500 cGy)	Remission x 4 months	49 wks

actino-D, actinomycin-D; adria, adriamycin; cis, cisplatin; carbo, carboplatin; CT, computerized tomography; GEM, gemcitabine; ifos, ifosphamide; LN, lymph node; mets, metastases; MVAC, methotrexate, vinblastine, doxorubicin and cisplatin; RN, radical nephrectomy; SFU, S-fluorouracil; THAL, thalidomide; U/S: ultrasound; VCN, vincristine; VP-16, etoposide; yo, year old.

metastatic disease work-up. Prior to the introduction of the active combination of PGC, survival from RMC was generally measured in weeks. With this new combination of chemotherapeutic agents, patients are having partial and, at times, complete responses. We surmise that local CNS recurrence may become a more common problem as these agents poorly cross the blood-brain barrier. CNS prophylaxis such as CSI, intrathecal chemotherapy, or a combination of cranial radiation and intrathecal chemotherapy may prevent or delay CNS recurrence. The majority of RMC patients present with widely metastatic disease and microscopic malignant cells may be more likely to respond completely to radiation therapy than bulky metastatic disease. Ideally, a randomized controlled trial with and without CSI in RMC would be conducted to definitively answer the question of whether CSI would be helpful to decrease the incidence of CNS recurrence. Due to the rarity of this tumor type, it is unlikely that a randomized trial can be done in a timely fashion. Radiation appears to be well tolerated in patients with RMC and the potential benefits may outweigh the risks in this group of patients. Therefore, CNS prophylactic therapy should be considered in patients with metastatic RMC to potentially improve the progression-free interval.

References

1. Walsh A, Kelly DR, Vaid YN, et al. Complete response to carboplatin, gemcitabine, and paclitaxel in a patient with advanced metastatic renal medullary carcinoma.

Pediatr Blood Cancer 2010;55:1217-20.
2. Davis CJ, Jr., Mostofi FK, Sesterhenn IA. Renal medullary carcinoma. The seventh sickle cell nephropathy. Am J Surg Pathol 1995;19:1-11.
3. Khan A, Thomas N, Costello B, et al. Renal medullary carcinoma: sonographic, computed tomography, magnetic resonance and angiographic findings. Eur J Radiol 2000;35:1-7.
4. Selby DM, Simon C, Foley JP, et al. Renal medullary carcinoma: can early diagnosis lead to long-term survival? J Urol 2000;163:1238.
5. Watanabe IC, Billis A, Guimaraes MS, et al. Renal medullary carcinoma: report of seven cases from Brazil. Mod Pathol 2007;20:914-20.
6. Schaeffer EM, Guzzo TJ, Furge KA, et al. Renal medullary carcinoma: molecular, pathological and clinical evidence for treatment with topoisomerase-inhibiting therapy. BJU Int 2010;106:62-5.
7. Cheng JX, Tretiakova M, Gong C, et al. Renal medullary carcinoma: rhabdoid features and the absence of INI1 expression as markers of aggressive behavior. Mod Pathol 2008;21:647-52.
8. Avery RA, Harris JE, Davis CJ, Jr., et al. Renal medullary carcinoma: clinical and therapeutic aspects of a newly described tumor. Cancer 1996;78:128-32.
9. Motzer RJ, Bacik J, Mariani T, et al. Treatment outcome and survival associated with metastatic renal cell carcinoma of non-clear-cell histology. J Clin Oncol 2002;20:2376-81.
10. Simpson L, He X, Pins M, et al. Renal medullary carcinoma and ABL gene amplification. J Urol 2005;173:1883-8.
11. Hakimi AA, Koi PT, Milhoua PM, et al. Renal medullary carcinoma: the Bronx experience. Urology 2007;70:878-82.
12. Strouse JJ, Spevak M, Mack AK, et al. Significant responses to platinum-based chemotherapy in renal medullary carcinoma. Pediatr Blood Cancer 2005;44:407-11.
13. Bell MD. Response to paclitaxel, gemcitabine, and cisplatin in renal medullary carcinoma. Pediatr Blood Cancer 2006;47:228.
14. Karaman S, Celkan T, Kuruoglu S, et al. Renal medullary carcinoma case presenting with abdominal mass. Turkish Journal of Cancer 2005;35:96-8.
15. Stahlschmidt J, Cullinane C, Roberts P, Picton SV. Renal medullary carcinoma: prolonged remission with chemotherapy, immunohistochemical characterisation and evidence of bcr/abl rearrangement. Med Pediatr Oncol 1999;33:551-7.
16. Rathmell WK, Monk JP. High-dose-intensity MVAC for Advanced Renal Medullary Carcinoma: Report of Three Cases and Literature Review. Urology 2008;72:659-63.
17. Pui CH, Thiel E. Central nervous system disease in hematologic malignancies: historical perspective and practical applications. Semin Oncol 2009;36:S2-S16.
18. Stinchcombe TE, Gore EM. Limited-stage small cell lung cancer: current chemoradiotherapy treatment paradigms. Oncologist 2010;15:187-95.
19. Dimashkieh H, Choe J, Mutema G. Renal medullary carcinoma: a report of 2 cases and review of the literature. Arch Pathol Lab Med 2003;127:e135-8.