JOURNAL OF CASE REPORTS 2014;4(2):320-323

Temsirolimus as a Prospective Treatment Option in Sarcomatoid Renal Cell Carcinoma

Manisha Singh
Consultant Medical Oncologist, Mahavir Cancer Sansthan, Patna, Bihar, India.

Abstract:

Renal cell carcinoma (RCC) consists of a heterogeneous group of tumors with distinct genetic and metabolic defects, as well as histopathologic and clinical features. RCC has an inclination for metastatic spread to uncommon sites, with an aggressive behaviour. Here, we share an unusual case of sarcomatoid RCC (sRCC) with lung metastasis, in a patient who underwent left-sided radical nephrectomy nearly 15 years ago. We used an emerging treatment option, with a positive outcome in the case.

Key words: Renal cell carcinoma, Nephrectomy, Kidney Neoplasms, Humans.

Introduction

Renal cell carcinoma (RCC) accounts for 90-95% of malignant neoplasms arising from the kidney and approximately 3% of all adult malignancies. In India, its incidence is 0.9% and mortality is 0.6% [1]. Histologically, the clear cell type, which arises from the proximal tubule, is the most common. Medullary carcinomas, being the rarest, are aggressive and are exclusively associated with sickle cell trait [2]. In sarcomatoid RCC (sRCC), metastatic disease is extremely common with 45-84% patients having evidence of systemic disease, because of their aggressive behaviour. It usually indicates a worse prognosis in patients as compared to those with even other high-grade RCCs, because of limited systemic therapy options, which have met with extremely poor results in the past [3].

Case Report

A 68-year-old male patient presented to us in January 2013 with right sided chest pain and cough since 2 months. He was a known case of hypertension for which he was on regular treatment. The patient had undergone a left radical nephrectomy about 15 years ago. Physical examination did not reveal anything significant, except bilateral jugulodigastric lymph node enlargement which was firm, non-mobile and non-tender.

The haematology and bio-chemistry reports did not reveal any significant abnormalities; however, the chest X-ray discovered an ill-defined inhomogeneous opacity in the right upper and middle zone centrally. This necessitated a prompt further evaluation of the same. Couple of days

Corresponding Author: Dr. Manisha Singh
Email: drmanishasingh111@gmail.com
Received: May 27, 2014 | **Accepted:** August 5, 2014 | **Published Online:** August 25, 2014

Conflict of interest: None declared | **Source of funding:** Nil | **DOI:** http://dx.doi.org/10.17659/01.2014.0080

later, CT scan of the thorax was performed and it revealed what we had anticipated – a large (about 8x7x4 cm) heterogeneously enhancing lesion involving right lung upper lobe [Fig.1].

The radiologist suggested that the lesion looked doubtful for which an immediate cytology correlation was suggested. A CT guided FNAC from the mass was opted for, the results of which suggested metastatic carcinoma, secondary to a RCC.

Having undergone a left radical nephrectomy about 15 years ago, this was his 2nd malignancy which was sarcomatoid in nature with infiltration to perirenal fat and capsule. Laboratory tests were within normal limits, except LDH, which was 2639 U/L. Let us see what the outcome of the case was and how we achieved it.

Discussion

Histologically, sRCC depicts features similar to sarcomas-spindle-like cells, high cellularity, and cellular atypia with absence of epithelial components. However, they are extremely rare in adults, accounting for <1% of renal malignancies [3].

In sRCC cases, metastatic disease is extremely common with 45-84% patients having evidence of systemic disease. Most commonly, sRCC metastasizes to similar locations as other RCCs, the common sites being lungs, bone, nodes, liver, and brain [3]. The presence of sarcomatoid components indicates a worse prognosis. Patients who have RCC depicting sarcomatoid features have demonstrated limited responses to chemotherapy and immunotherapy with extremely poor results [3,4].

Prior to introduction of immunotherapy and molecular targeted therapy, nephrectomy was a palliative procedure without significant improvement

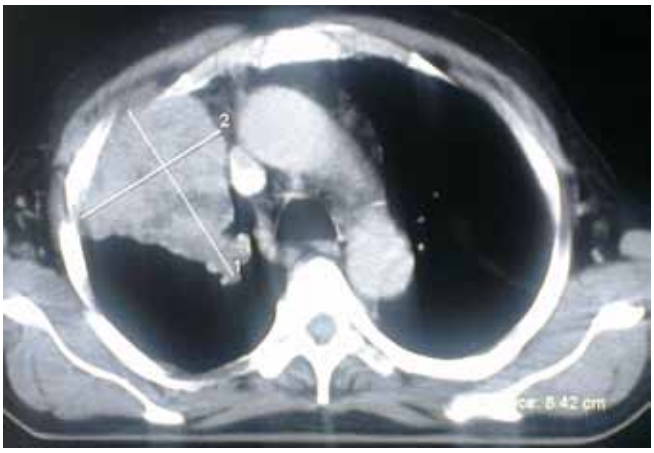

Fig.1: CT scan thorax in January 2013-Large solid mass in right upper lobe with calcification in superior mediastnum.

According to the National Comprehensive Cancer Network (NCCN) guidelines, following are the predictors of short survival used to select patients for Temsirolimus[12]:

1. Lactate dehydrogenase level > 1.5 times upper limit of normal
2. Haemoglobin level < lower limit of normal
3. Corrected serum calcium level >10 mg/dL (2.5 mmol/L)
4. Interval of less than a year from original diagnosis to the start of systemic therapy
5. Karnofsky performance score ≤ 70
6. ≥ 2 sites of organ metastasis

(Poor prognosis patients are defined as those with ≥3 predictors of short survival)

in overall survival. Some studies and authors have reported recurrence rates of as high as 93% within 5 years of nephrectomy, and sometimes as late as 30 years after surgery [5,6]. Because of distinct pathology involved in sRCC, molecular targeted therapy can be a promising treatment option. Clear cell carcinoma, which is the most common histological variant, is associated with loss of function of the von Hippel Lindau gene. This leads to hypoxia, angiogenesis and increased vascularity of the tumor and metastases through the hypoxia inducible factor (HIF) and the vascular endothelial growth factor (VEGF) [7]. One of the critical steps

in the growth, invasion and metastatic spread of tumours is angiogenesis [8].

This pathology was evaluated by Tickoo SK and colleagues in sarcomatoid regions of tumours with clear cell origin. These tumours demonstrated high HIF pathway expression in the sarcomatoid regions, whereas those from non-clear cell tumours continued to have limited expression. These findings suggest a common cell of origin/common biology between tumor components and that targeted VEGF agents could play a positive role in sRCC treatment [9].

Temsirolimus (CCI-779) is an inhibitor of mammalian target of rapamycin (mTOR), which is involved in the growth and proliferation of cells and their response to hypoxic stress [10]. When the kinase activity of mTOR is activated, the synthesis of cell cycle proteins and HIF are increased. HIF then stimulates VEGF and thereby, angiogenesis which is very critical in pathogenesis of RCC [11]. An intracellular protein, FK BP12 found in abundance, binds to temsirolimus forming a complex that inhibits mTOR signaling. This suppresses the production of proteins that regulate progression through the cell cycle and angiogenesis [10].

According to NCCN 2014 guidelines, temsirolimus is a category 1 recommendation for clear cell carcinoma in poor-risk patients and non-clear cell histology [12]. In a randomised trial involving 626 patients with poor-prognosis metastatic RCC, median overall survival time for temsirolimus was 10.9 months which was better and statistically significant when compared to the interferon alone group (7.3 months) and the combination of interferon and temsirolimus group (8.4 months) [10]. Areses MC and colleagues presented few cases of RCC with sarcomatoid differentiation treated with temsirolimus. One of the cases showed clinical improvement and a partial response to lung metastasis and another case was evaluated as stable disease after 7 months [13].

In this case, the patient was initially treated with pemetrexed but the response to therapy was unsatisfactory. After intensive discussion and analysis, he was later administered temsirolimus 25 mg, with very good symptomatic response in just 5 cycles. An excellent response was observed, with almost total remission during the 9th cycle [Fig. 2]

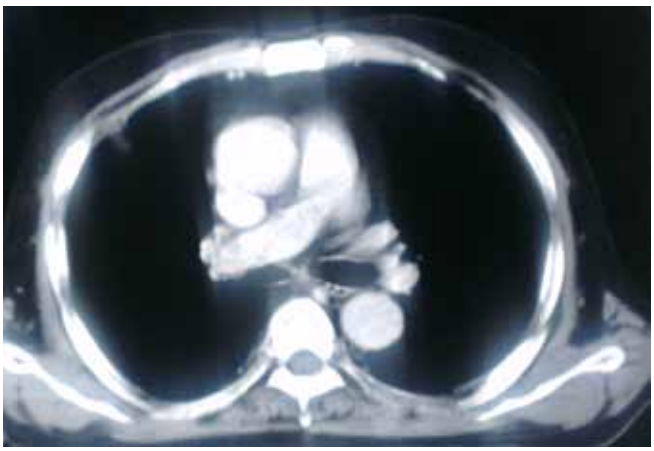

Fig. 2: CT scan thorax in October 2013 - Near total remission of the mass.

Conclusion

The result of this case study points towards the use of molecular targeted therapeutic agents in the treatment of sarcomatoid type of RCC, temsirolimus being one of them. Temsirolimus must be considered as prospective and effective first-line treatment for metastatic RCC with sarcomatoid differentiation. However, decisions regarding its use in specific cases must be at the physician's discretion and previous experience, if any.

Clinical Pointers:

1. Radical nephrectomy cannot prevent recurrence of metastatic RCC
2. Unsatisfactory response to premetrexed alone.
3. Successful use of mTOR inhibitor, temsirolimus in improving survival in sarcomatoid RCC.

References

1. International Agency for Cancer Research, WHO. The Globocan Project, Globocan 2008; Available from http://globocan.iarc.fr/factsheet.asp. Accessed on 4th Dec. 2013.
2. Chittoria N, Rini B. Renal Cell Carcinoma. Cleveland Clinic center for continuing education; Available from http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/nephrology/renal-cell-carcinoma/#s0050. Accessed on 18th Nov. 2013.
3. Shuch B, Bratslavsky G, Linehan WM, Srinivasan R. Sarcomatoid renal cell carcinoma: a comprehensive review of the biology and current treatment strategies. Oncologist. 2012;17(1):46-54.
4. Golshayan AR, George S. Metastatic sarcomatoid renal cell carcinoma treated with vascular endothelial growth factor-targeted therapy. J Clin Oncol 2009;27(2):235-241.
5. McNichols DW, Segura JW, DeWeerd JH. Renal cell carcinoma: long-term survival and late recurrence. J Urol 1981;126(1):17-23.
6. Ljungberg B, Alamdari FI, Rasmuson T, Roos G. Follow-up guidelines for nonmetastatic renal cell carcinoma based on the occurrence of metastases after radical nephrectomy. BJU Int 1999;84(4):405-411.
7. Xia G, Kageyama Y, Hayashi T, Kawakami S, Yoshida M, Kihara K. Regulation of vascular endothelial growth factor transcription by endothelial PAS domain protein 1 (EPAS1) and possible involvement of EPAS1 in the angiogenesis of renal cell carcinoma. Cancer 2001;91:1429-1436.
8. Ather MH, Masood N, Siddiqui T. Current management of advanced and metastatic renal cell carcinoma. Urol J 2010;7(1):1-9.
9. Tickoo SK, Alden D, Olgac S, Fine SW, Russo P, Kondagunta GV, *et al*. Immunohistochemical expression of hypoxia inducible factor-1α and its downstream molecules in sarcomatoid renal cell carcinoma. J Urol 2007;177:1258-1263.
10. Hudes G, Carducci M, *et al*. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356(22):2271-2281.
11. Hudson CC, Liu M, Chiang GG, Otterness DM, Loomis DC, Kaper F, Giaccia AJ, Abraham RT. Regulation of hypoxia-inducible factor 1alpha expression and function by the mammalian target of rapamycin. Mol Cell Biol 2002;22(20):7004-7014.
12. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Kidney Cancer, Version 3.2014; Available from http://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed on 16th June 2014.
13. Areses MC, Herranz UA, Ferrán BB, Mateos LL, González JG, López RL. Temsirolimus in renal cell carcinoma with sarcomatoid differentiation: a report of three cases. Med Oncol 2012;29(2):795-798.