

Case Report

Case Report of Prolonged Stable Disease with Modified Schedule Sunitinib in Metastatic Renal Cell Carcinoma

Abstract

Background:

New targeted therapies have revolutionized the treatment landscape of metastatic renal cell carcinoma over the last decade. Sunitinib has demonstrated high activity in renal cell carcinoma (RCC), still complete remission is not a common occurrence in patients. In patient achieving complete response, continuation of therapy beyond complete response is debatable.

Cytoreductive nephrectomy has shown to be beneficial in metastatic renal cell carcinoma in patients treated with interferon. However, its role is not established in targeted therapy era.

Case Presentation: A patient was diagnosed with renal clear cell carcinoma with multiple pulmonary metastases. He underwent cytoreductive nephrectomy and was started Sunitinib post-operatively. He experienced toxicities which were manageable with dose adjustments. He showed significant improvement on sunitinib therapy demonstrating complete response after total 22 months of therapy. After careful consideration and discussion with patient, sunitinib was stopped. Patient continues to be in excellent condition after stopping Sunitinib.

Conclusions: This case highlights that complete response can be achieved by sunitinib post cytoreductive nephrectomy with good quality of life and manageable toxicities. The case also highlights that discontinuation of therapy can be an option for some patients.

Keywords: Complete response, Sunitinib, Renal cell cancer, Cytoreductive nephrectomy

25 **Background**

26 Sunitinib is an orally administered multitarget tyrosine kinase inhibitor (TKI) used as a first
 27 line therapy for mRCC, which demonstrated longer progression-free survival (PFS), higher
 28 response rates and longer overall survival than interferon alfa. Partial response is reported in
 29 about 31-44 % of patients treated with sunitinib but complete response is reported in only
 30 about 3% of cases. (4,5). Upon attaining complete response, continuation or discontinuation
 31 of sunitinib is debatable.

32

33 Cytoreductive nephrectomy followed by immunotherapy has shown to be beneficial in the
 34 treatment of metastatic renal cancer (1, 2). However, these studies had evaluated interferon
 35 based immunotherapy. Current therapy for metastatic renal cell carcinoma (mRCC) mainly
 36 includes use of the targeted agents (3) and role of cytoreductive nephrectomy needs to be
 37 evaluated.

38

39 **Case Presentation**

40 A 68 year old, diabetic patient with history of past coronary artery bypass grafting presented
 41 in July 2008 with complains of low grade fever & weight loss since one month. The positron
 42 emission tomography scan showed intensely FDG (fluorodeoxyglucose) avid mass in the
 43 right kidney which was likely to be mitotic accompanied by multiple pulmonary, pleural &
 44 crural metastases along with left pleural effusion. The computed tomography (CT) scan of
 45 chest revealed pleural effusion with nodular pleural thickening on left side (Figure 1). His
 46 echocardiograph was normal for the left ventricular ejection fraction. Baseline performance
 47 score was two.



48

49

50 Figure 1: Computed tomography scan showing bilateral lung involvement

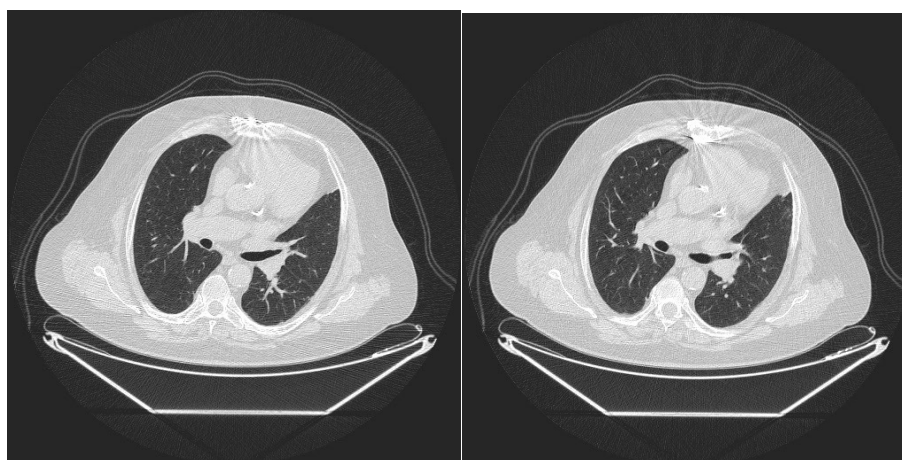
51 The patient was subjected to pleural tap in July 2008, which confirmed malignant cells. Right
 52 radical nephrectomy was done with the pathological diagnosis of moderately differentiated
 53 renal clear cell carcinoma extending to renal pelvis and peripelvic adipose tissue and
 54 revealing tumor emboli in many lymphovascular spaces.

55 Post-operatively, in July 2008, patient was started on Sunitinib 50 mg daily for 4 weeks of
 56 treatment followed by 2-weeks-off (Schedule 4/2). September 2008, patient reported shortness
 57 of breath, hence the dose was reduced to 37.5 mg in 4/2 schedule. In November 2008, patient
 58 had developed dyspnea at rest. CECT Thorax revealed irregular nodular soft tissue deposits
 59 in the left pleura and increased left pleural effusion & persistent enlarged left hilar lymph
 60 nodes& tiny nodular lesions in bilateral lungs. Sunitinib was stopped.

61 CECT done in January 2009, showed regression of pleural disease, left hilar lymph nodes and
 62 left pleural effusion. Sunitinib was restarted at dose of 25mg (schedule 4/2). Patient reported
 63 improvement in his symptoms on dose reduction.

64 After receiving therapy for another 16 months, patients stopped Sunitinib in May 2011.

65 Follow up PET scan in September 2011, revealed complete response (Figure 2)



66
67 Figure 2: PET scan in September 2011 showing complete response

68 Patient is still maintaining complete remission, excellent overall health and performance
69 status.

70 Discussion

71 Our case demonstrates achievement of complete response with Sunitinib and prolonged
72 sustained complete response even after stopping Sunitinib. Although complete remission
73 (CR) is uncommon during treatment for mRCC with tyrosine kinase inhibitors (TKIs), it may
74 occur in few patient (<3%) patients (5). In a multicenteric, retrospective analysis of 64
75 patients with mRCC who achieved CR during treatment with TKI either Sunitinib or
76 Sorafenib, 36 patients had received TKI treatment alone and 28 had also received local
77 treatment. Most of the patients were of favorable or intermediate risk. Though total number
78 of patient treated with either TKI is not available, at main center only 1.7% (6 out of 353) of
79 patients achieved CR (9).

80

81 In our case, dilemma was about the continuation or discontinuation of Sunitinib after
 82 attaining complete response. In the pivotal phase III studies of sunitinib in metastatic renal
 83 cell carcinoma (mRCC), treatment was continued until the occurrence of disease progression
 84 or unacceptable adverse effects (or death) (4, 5). In Albeigs et al study, 36 patients who had
 85 attained CR with TKI alone, eight patients continued TKI treatment after CR whereas 28
 86 stopped treatment. 17 patients were in CR after 255 days of follow up. For 28 patients of
 87 TKI plus local treatment, 12 out of 25 patients, who stopped TKI, were in CR after 322 days
 88 follow up (9).

89

90 Possibility of having residual cancer cells left behind even after attainment of CR where
 91 discontinuation may allow the cells to proliferate and lead to disease recurrence, can be an
 92 argument for continuation. Continued therapy can maintain therapeutic pressure on the
 93 residual cancer cells. Authors have also mentioned rebound effect, with rapid regrowth and
 94 development of metastases observed after treatment discontinuation with TKIs which has
 95 been observed in preclinical models. Discontinuation of therapy could be argued to avoid
 96 toxicity and to avoid development of resistance (9).

97

98 Another report evaluated the outcome of 5 RC patients achieving CR with sunitinib and later
 99 discontinued sunitinib. After one year of stopping, 2 patients were still in CR, 3 patients
 100 relapsed at 3, 12 and 15 months (10).

101 Another case report discussed attainment of complete response with sunitinib, given for renal
 102 cell cancer recurrence in native kidney after renal transplantation. Eight cycles of
 103 preoperative Sunitinib lead to 33% tumor size reduction. Post-surgery, Sunitinib was given
 104 for total of 11 months. Complete response was attained in 9 months. Authors had given

Sunitinib for additional one course before discontinuation. Complete response was maintained for 2 years during follow up (11).

Cytoreductive nephrectomy has shown to be beneficial in mRCC. Studies by Flanigan RC,*et al.* & Mickisch G H,*et al.* showed benefit of Cytoreductive nephrectomy in mRCC. Flanigan *et al* reported in 331 patients, cytoreductive nephrectomy plus interferon α compared with interferon α alone with resectable primary tumor and reported a median survival of 13.6 months for nephrectomy plus interferon versus 7.8 months for interferon alone (1). Mickisch GH, *et al.* reported radical nephrectomy done before interferon therapy improved overall survival compared with interferon alone (17 vs 7 months) (2). Both studies demonstrated benefits mainly in patients with good performance status and lung metastasis. Since both trials were published in immunotherapy era, similar question needs to be answered with respect to targeted agents (3)

In 2014, Genitourinary Cancers Symposium, Heng D Y C, *et al* presented data of mRCC patients undergone cytoreductive nephrectomy versus no nephrectomy. Median overall survival in the former group was 20.6 months as compared to 9.5 months observed in later group ($p < 0.0001$) (6). A retrospective analysis conducted by Choueiri T K, *et al* suggests that the efficacy of TKIs is greater in nephrectomised mRCC. The cytoreductive nephrectomy was associated with a median overall survival of 19.8 months compared to 9.4 months for patients who did not undergo cytoreductive nephrectomy (7).

Currently there are two largely awaited randomized trials in mRCC patients to address the question. CARMENA (NCT00930033) will compare nephrectomy followed by sunitinib

128 versus sunitinib alone whereas EORTC 30073 trial (NCT01099423) will compare upfront or
129 delayed nephrectomy with sunitinib. (8)

130 Conclusions

131 We report a case of cytoreductive nephrectomy followed by sunitinib treatment. Sunitinib
132 lead to CR, patient stopped Sunitinib upon achieving CR and still in CR (60 months since
133 sunitinib is stopped). Both the options based on the existing data were explained to patient.
134 Patient favored discontinuation for lack of recommendations for continuation and lack of
135 negative data for discontinuation. Sunitinib shows acceptable tolerability and manageable side
136 effects. Such prolonged CR has not been reported after discontinuation of Sunitinib.
137 Therapeutic efficacy of TKIs after cytoreductive nephrectomy needs to be studied in the
138 wider population. Results of CARMENA and EORTC will help address the role of
139 cytoreductive nephrectomy in the era of targeted therapy in mRCC.

140 References

- 141 1. Flanigan RC, Salmon SE, Blumenstein BA, *et al.* Nephrectomy followed by
142 interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell
143 cancer. *N Engl J Med* 2001; 345(23): 1655–1659.
- 144 2. Mickisch GH, Garin A, van Poppel H, *et al.* Radical nephrectomy plus interferon-
145 alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-
146 cell carcinoma: a randomised trial. *Lancet* 2001; 358(9286): 966–970.
- 147 3. Escudier B, Eisen T, Porta C, *et al.* Renal cell carcinoma: ESMO Clinical Practice
148 Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2012;23
149 (Supplement 7): vii65–vii71.
- 150 4. Motzer RJ, Hutson TE, Tomczak P, *et al.* Sunitinib versus interferon alfa in metastatic
151 renal cell carcinoma. *N Engl J Med* 2007;356:115-124.
- 152 5. Motzer RJ, Hutson TE, Tomczak P, *et al.* Overall survival and updated results for
153 sunitinib compared with interferon alfa in patients with metastatic renal cell

- 154 carcinoma. *J Clin Oncol.* 2009 Aug 1;27(22):3584-90. doi:
155 10.1200/JCO.2008.20.1293.
- 156 6. Heng DY, Rini BI, Beuselinck B, et al: Cytoreductive nephrectomy (CN) in patients
157 with synchronous metastases from renal cell carcinoma: Results from the
158 International Metastatic Renal Cell Carcinoma Database Consortium (IMDC).
159 Genitourinary Cancers Symposium. [Abstract 396](#). Presented February 1, 2014.
- 160 7. Choueiri TK, Xie W, Kollmannsberger CK *et al.* The impact of cytoreductive
161 nephrectomy in patients with metastatic renal cell carcinoma (mRCC) treated with
162 vascular endothelial growth factor (VEGF)-targeted therapy. *J Urol.* 2011
163 Jan;185(1):60-6.
- 164 8. ClinicalTrials.gov. 2014 <https://clinicaltrials.gov> (as accessed on 30 August, 2014)
- 165 9. Albiges L, Oudard S, Negrier S, *et al.* Complete remission with tyrosine kinase
166 inhibitors in renal cell carcinoma. *Journal of Clinical Oncology* 2012;30(5):482-487.
167 .
- 168 10. Demiselle J, Lheureux S, Clarisse B, *et al.* Metastatic renal cancer: Evolution of five
169 complete response cases after the antiangiogenic discontinuation. *Bulletin du Cancer*,
170 2011, 98: 626-632
- 171 11. Hongo F, Oishi M, Ueda T, *et al.* Complete response of sunitinib therapy for renal
172 cell cancer recurrence in the native kidney after renal transplantation: a case report.
173 *BMC Res Notes.* 2014 Aug 13;7:526. doi: 10.1186/1756-0500-7-526.