

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

BACKGROUND

27 Cytoreductive nephrectomy followed by immunotherapy has shown to be beneficial in the treatment of
28 metastatic renal cancer (1, 2). However, these studies had evaluated interferon based
29 immunotherapy. Current therapy for metastatic renal cell carcinoma (mRCC) mainly includes use of
30 the targeted agents (3) and, thus, the role of cytoreductive nephrectomy needs to be re-evaluated (in
31 conjunction with targeted agents).

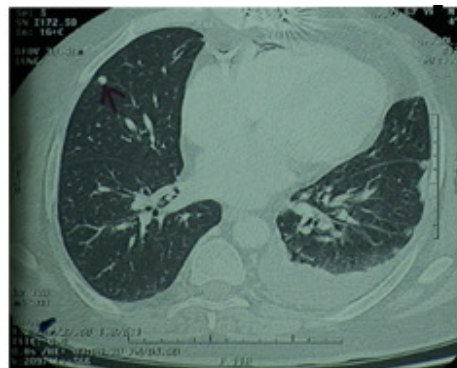
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33 Sunitinib is an orally administered multitarget tyrosine kinase inhibitor (TKI) used as a first line therapy
34 for mRCC, which demonstrated longer progression-free survival (PFS), higher response rates and
35 longer overall survival than interferon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

38

39 CASE PRESENTATION

40 A 68 year old, diabetic patient with history of past coronary artery bypass grafting presented in July
41 2008 with complaints of low grade fever & weight loss since one month. The computed tomography
42 (CT) scans showed left sided renal mass with metastatic spread to pleura and lungs (Figure 1). His
43 echocardiograph was normal for the left ventricular ejection fraction and his baseline performance
44 score was two.



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46 **Figure 1: CT scans showing left sided renal mass with bilateral lung involvement**

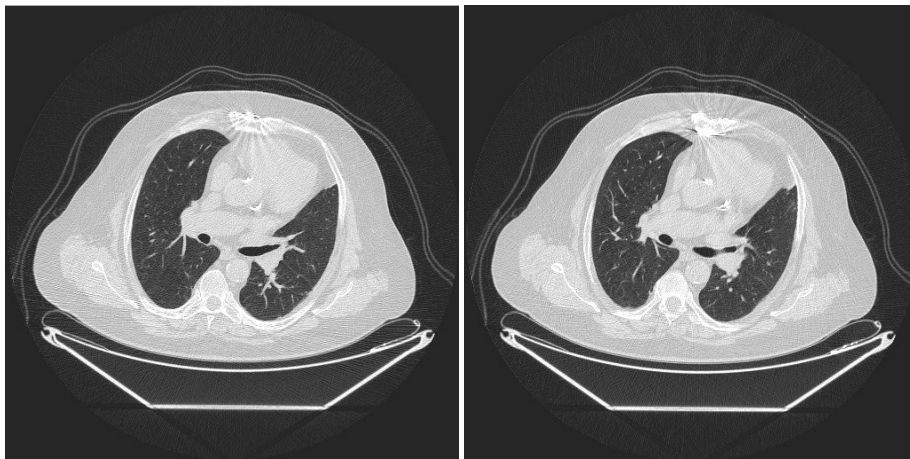
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48 The patient was subjected to pleural tap in July 2008, which confirmed malignant cells. Left radical
49 nephrectomy was done with the pathological diagnosis of moderately differentiated renal clear cell
50 carcinoma extending to renal pelvis and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

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

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

61 After receiving therapy for another 16 months, patients stopped Sunitinib in May 2011. Follow up PET
62 scan in September 2011, revealed complete response (Figure 2)



63
64 **Figure 2: PET scan in September 2011 showing complete response**

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66 Patient is still maintaining complete remission, excellent overall health and 0 performance status.

67 DISCUSSION

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

76

77 In our case, the dilemma was about the continuation or discontinuation of Sunitinib after attaining
78 complete response. In the pivotal phase III studies of sunitinib in metastatic renal cell carcinoma
79 (mRCC), treatment was continued until the occurrence of disease progression or unacceptable
80 adverse effects (or death) (4, 5). The possibility of having residual cancer cells left behind even after
81 attainment of CR where discontinuation may allow the cells to proliferate and lead to disease
82 recurrence, can be an argument for continuation. Continued therapy can maintain therapeutic
83 pressure on the residual cancer cells. Authors have also mentioned rebound effect, with rapid
84 regrowth and development of metastases observed after treatment discontinuation with TKIs which
85 has been observed in preclinical models. Discontinuation of therapy could be argued to avoid toxicity
86 and to avoid development of resistance (6).

87

88 Another report evaluated the outcome of 5 renal cancer patients achieving CR with sunitinib and later
89 discontinued sunitinib. After one year of stopping, 2 patients were still in CR, 3 patients had relapsed
90 at 3, 12 and 15 months (7).

91 Another case report discussed attainment of complete response with sunitinib, given for renal cell
92 cancer recurrence in native kidney after renal transplantation. Eight cycles of preoperative Sunitinib
93 lead to 33% tumor size reduction. Post-surgery, Sunitinib was given for total of 11 months. Complete
94 response was attained in 9 months. Authors had given Sunitinib for additional one course before
95 discontinuation. Complete response was maintained for 2 years during follow up (8).

96

97 Cytoreductive nephrectomy has shown to be beneficial in mRCC. Studies by Flanigan RC,*et al.* &
98 Mickisch G H,*et al.* showed benefit of cytoreductive nephrectomy in mRCC. Flanigan et al studied in
99 331 patients, cytoreductive nephrectomy plus interferon α compared with interferon α alone with
100 resectable primary tumor and reported a median survival of 13.6 months for nephrectomy plus
101 interferon versus 7.8 months for interferon alone (1). Mickisch GH, *et al.* reported that radical
102 nephrectomy done before interferon therapy improved overall survival compared with interferon alone
103 (17 vs 7 months) (2). Both studies demonstrated benefits mainly in patients with good performance
104 status and lung metastasis. Since both trials were published in immunotherapy era, similar question
105 needs to be answered with respect to targeted agents (3).

106 In 2014, Genitourinary Cancers Symposium, Heng D Y C, et al presented data of mRCC patients
107 undergone cytoreductive nephrectomy versus no nephrectomy. Median overall survival in the former
108 group was 20.6 months as compared to 9.5 months observed in later group ($p < 0.0001$) (9). A
109 retrospective analysis conducted by Choueiri T K, *et al* suggests that the efficacy of TKIs is greater in
110 nephrectomised mRCC. The cytoreductive nephrectomy was associated with a median overall
111 survival of 19.8 months compared to 9.4 months for patients who did not undergo cytoreductive
112 nephrectomy (10).

113

114 Currently there are two largely awaited randomized trials in mRCC patients to address the question.
115 CARMENA (NCT00930033) will compare nephrectomy followed by sunitinib versus sunitinib alone
116 whereas EORTC 30073 trial (NCT01099423) will compare upfront or delayed nephrectomy with
117 sunitinib (11).

118

119 **CONCLUSIONS**

120 We report here a case of cytoreductive nephrectomy followed by sunitinib treatment. In this case
121 Sunitinib led to CR and the patient stopped Sunitinib upon achieving CR and still continues to be in
122 CR (60 months since sunitinib is stopped). Both the options based on the existing data were
123 explained to patient. Patient favored discontinuation for lack of recommendations for continuation and
124 lack of negative data for discontinuation. Sunitinib shows acceptable tolerability and manageable side

effects. Such prolonged CR has not been reported after discontinuation of Sunitinib. Therapeutic efficacy of TKIs after cytoreductive nephrectomy needs to be studied in a wider population. Results of CARMENA and EORTC will help address the role of cytoreductive nephrectomy in the era of targeted therapy in mRCC.

CONSENT DISCLAIMER AND ETHICAL APPROVAL:

Not applicable.

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