

# Prolonged response to cytoreductive surgery and sunitinib in an elderly patient with synchronous multiple metastases from renal cell carcinoma

Maria Cristina Locatelli<sup>1</sup>, Aurora Miedico<sup>1</sup>, Adelaide D'Antona<sup>1</sup>, Giovanni Longo<sup>2</sup>, Matteo Maggioni<sup>2</sup>, Augusto Maggioni<sup>3</sup>, Pietro Tombolini<sup>2</sup>, and Donata Tabiaddon<sup>1</sup>

<sup>1</sup>Department of Oncology, and <sup>2</sup>Department of Urology, San Carlo Borromeo Hospital, Milan;

<sup>3</sup>Department of Urology, Università degli Studi Milano, Milan, Italy

---

## ABSTRACT

One third of patients with renal cell cancer have metastatic disease at diagnosis. Until now the outcome of these patients has been poor due to the variable natural history of the disease and the lack of effective therapy. Multitargeted therapy of advanced renal cell cancer appears to be a better option than immunotherapy. We report the case of an elderly patient with skin, lung, bone and brain metastases and widespread intraabdominal disease treated with cytoreductive surgery and sunitinib, resulting in a prolonged response. Free full text available at [www.tumorionline.it](http://www.tumorionline.it)

---

## Introduction

Renal cell carcinoma (RCC) is a cancer with a relatively low incidence, accounting for about 2-3% of all cancers. In the last 2 decades an increase in RCC has been observed due to the widespread utilization of abdominal ultrasonography. Notwithstanding its early detection, one third of patients have metastatic disease at diagnosis<sup>1</sup>. Until now the outcome of these patients has been poor as a result of the variable natural history of RCC and the lack of effective systemic therapy.

Multitargeted therapy of advanced RCC appears to be a better option than immunotherapy. Sunitinib is a multitarget tyrosine kinase inhibitor whose activity has been demonstrated in phase III and expanded-access studies. In the present paper we report the case of an elderly patient with multiple metastases who attained a prolonged response to sunitinib.

## Case report

A 72-year-old woman with a Karnofsky performance status of 90, no significant medical history, and no comorbidities but hypertension treated with transdermal clonidine (TTS-1) was referred to our hospital in October 2006 complaining of flank pain and gross hematuria. At clinical examination a mass in the right flank and a 2-cm subcutaneous nodule in the right breast were detected. Total-body CT scan showed a right kidney neoplasm of 15 cm, a mass in the left adrenal gland, peripancreatic abnormal tissue, small lung nodules (3 bilateral nodules of 1 cm) and extensive hilar-mediastinal lymphadenopathies (max diameter 3.8 cm). At cranial CT evaluation a subcentimetric (0.4 cm) thalamic lesion of uncertain etiology was identified. Bone scintigraphy was normal. At blood chemistry mild anemia (Hb 11.7 g/dL) was present; LDH and calcium were in the normal range. Surgical excision of the subcutaneous breast nodule revealed an adenocarcinoma of metastatic origin.

Considering the good performance status of the patient, the absence of serious comorbidity, the intermediate Motzer risk group but the presence of symptoms due to the renal mass, she underwent a right radical nephrectomy and abdominal cytore-

**Key words:** sunitinib, renal cell cancer, target therapies, elderly patient.

*Correspondence to:* Dr Maria Cristina Locatelli, Divisione di Oncologia Medica, Ospedale San Carlo Borromeo, Via Pio II, 3 -20123- Milano, Italy.  
Tel +39-02-40222255;  
e-mail [locatellimc@hotmail.com](mailto:locatellimc@hotmail.com)

Received August 31, 2009;  
accepted November 17, 2009.

ductive surgery including left adrenalectomy and distal pancreatectomy. No residual intraabdominal gross tumor remained after surgery. Final pathology documented a 15 × 10 × 8 cm clear cell RCC, Fuhrman grade 2, pT3cN0M1, with pancreatic and contralateral adrenal involvement. After surgery the patient recovered quickly and was placed on chronic corticosteroid treatment. Four weeks later (December 2006) she began subcutaneous interferon-alfa (IFN) 6 MU three times/weekly; higher doses were not tolerated. In February 2007, treatment was discontinued because of malaise and bone pain in the left hip. A CT scan of the pelvis revealed bone involvement at the left ischium. On CT and MRI the thalamic lesion was found to have increased to 1 cm with peripheral edema. The patient underwent stereotactic radiosurgery (Cyberknife) of the brain lesion. After cardiological assessment with ECG and echocardiography, in April 2007 she was placed on sunitinib 50 mg daily in a 6-week cycle according to a 4/6 schedule (4 weeks on treatment, 2 weeks off treatment). Follow-up visits and blood chemistry were planned every 2 weeks and the patient was instructed to monitor her blood pressure 3 times a week. Echocardiographic exams were planned every 3 months. After the second cycle, during an intercurrent febrile episode with vomiting and diarrhea, the patient developed reversible acute renal failure (creatinine 8 mg/dL) with severe electrolyte imbalance (hyperkalemia 8 mEq/mL) requiring hospitalization. Grade 3 hypertension required treatment with 2 drugs, clonidine and amlodipine, which has a low CYP3A4 metabolism; hydrochlorothiazide was avoided because of the renal failure. After resolution of the episode, with creatinine levels ranging from 1.6 to 2.28 mg/dL, sunitinib was administered at a reduced dose of 37.5 mg/day with the usual 4/6 week schedule.

In June 2007, despite a CT scan showing mild progression of the intrathoracic lesions (Figure 1) and the onset of symptomatic pelvic bone involvement (but no abnormalities on bone scan), sunitinib was continued with no dose or schedule variation.

In November 2007 total-body CT documented complete remission of the lung nodules, partial remission (according to the RECIST criteria) of the hilar-mediastinal metastases (Figure 2), reduction of the extraosseous component of the bone involvement with resolution of pain, and stabilization of the brain lesion. The patient continued sunitinib at the same dose and schedule. Toxicity consisted of mild asthenia, mild dysgeusia, grade 1 hand-foot syndrome, pale yellow cutaneous pigmentation, and mild neutropenia. Hypertension was controlled by the 2-drug combination, requiring only an increase in the dose of amlodipine (10 mg) during the 4 weeks of sunitinib administration.

In January 2008 the patient was hospitalized again because of the very rapid onset (a few hours) of a severe episode of diarrhea due to a minor *Salmonella* infection, related adrenal insufficiency, and hypovolemic



Figure 1 - CT image: intrathoracic lesions during the early phase of sunitinib treatment.



Figure 2 - CT image: response of intrathoracic lesions after 14 months of sunitinib treatment.

shock. Sunitinib was interrupted for 8 weeks until complete recovery. Sunitinib therapy was resumed after the resolution of severe asthenia. In June 2008 a CT scan revealed persistent complete remission of the lung lesions, partial remission of the hilar-mediastinal nodes and bone lesions, and stability of the brain metastasis.

In August 2008 she developed gastric symptoms including pain and vomiting after food intake. CT scan revealed a retroduodenal adenopathic mass causing duodenal substenosis, and progression of the intrathoracic disease. Considering the patient's performance status (ECOG 1) and the long-lasting response, after cardiological and thyroid reassessment we decided to continue

with sunitinib treatment at an increased dose (50 mg daily, 4/6 weeks). In December 2008 a CT scan showed a partial response of both the intrathoracic and abdominal disease (Figure 3), with complete resolution of abdominal pain and a return to normal food intake. A partial response of the mediastinal nodes followed in April 2009 (Figure 4). Toxicity increased with grade 3 hypertension, which was controlled by administration of hydrochlorothiazide 12.5 mg as the third antihypertensive drug, and worsening of asthenia and hyporexia.

Up to now (June 2009) the patient is continuing sunitinib treatment and there is good control of arterial blood pressure with the 3-drug combination, no electrocardiographic or echocardiographic alterations, normal thyroid function, grade 1 leukopenia and thrombocytopenia, and macrocytosis. The patient is in good performance status (Karnofsky 80) and asymptomatic, but complaining of asthenia especially during the 4 weeks

of sunitinib administration, causing mild impairment of quality of life.

## Discussion

The role of surgery in metastatic RCC is still debatable especially in this new era of targeted therapy. Cytoreductive nephrectomy has been found useful in prolonging survival in patients with synchronous metastases treated with cytokines<sup>1</sup> and is considered a valuable option; moreover, it has the advantage of removing symptoms related to a renal mass. In case of a single metastatic site, especially the lung, surgical removal is probably the best option, with a 5-year survival of up to 54%<sup>2,3</sup>, but when there are multiple metastases even patients undergoing complete resection fare worse, and the prognosis is even more disappointing if the resection is incomplete<sup>2,4</sup>. A recent analysis of patients submitted to multiple metastasectomy showed a positive impact on survival in patients with a good/intermediate prognosis<sup>5</sup>, but this approach needs confirmation. Also, in a sunitinib expanded-access trial the antitumor activity of the drug was similar for patients submitted to nephrectomy or not<sup>6</sup>. At the time of our patient's diagnosis no data were available and we opted for nephrectomy and intraabdominal cytoreduction for symptomatic palliation; we took into account the patient's good performance status and possible macroscopic complete intraabdominal cytoreduction with a residual metastatic burden limited to the lungs. Nephrectomy is debated also in the presence of metastatic disease to the brain, but at the time of surgery our patient presented a small subcentimetric lesion of uncertain etiology.

Regarding the treatment of CNS lesions, the probability of the disappearance of CNS metastasis with radiotherapy is low, but growth control is good and it is regarded as a valid option in renal cancer. We chose to give radiotherapy before medical treatment because of the potential risk of bleeding during sunitinib administration<sup>7</sup> and of progression of the lesion. In fact, the prognosis of patients with widespread metastases including the brain is generally dismal and treatment with antiangiogenic drugs in this subset of patients is controversial. The expanded-access program of sunitinib included patients with CNS involvement and retrospective analysis shows safety data similar to those of patients without brain metastases<sup>8</sup>. Efficacy of sunitinib against CNS metastasis has been reported<sup>9</sup> but is not evaluable in our case because the patient was treated by Cyberknife.

Sunitinib is a multitarget tyrosine kinase inhibitor with proven activity in phase II-III and expanded-access studies in patients with multiple metastases; it was confirmed to be associated with longer median progression-free survival than IFN<sup>10</sup>. It is effective even as second line treatment after cytokines and yields a high rate of partial remissions. It is administered orally and pro-



Figure 3 - CT image: intraabdominal response to sunitinib at a dose of 50 mg.



Figure 4 - CT image: intrathoracic response to sunitinib at a dose of 50 mg.

longed responses (>6 months) have been reported in both naïve and pre-treated patients<sup>11</sup>. This is the reason we selected this drug after IFN failure, and we obtained a long-lasting partial response of the intrathoracic disease, shrinkage of the bone lesion with resolution of pain, and control of residual microscopic peritoneal and retroperitoneal involvement.

Adequate dose administration is a crucial issue during sunitinib treatment because the chances of partial or complete remission appear directly related to drug peaks. We opted for a reduced dose after the first cycle because the patient developed not easily manageable hypertension and renal impairment, in spite of appropriate monitoring and supportive care. It is meaningful that at disease progression with symptomatic disease the patient responded again after only 2 cycles at the optimal dose of 50 mg. The patient has been alive for almost 3 years from the diagnosis and more than 2 years after the start of sunitinib treatment in spite of the presence of multiple metastases. Other cases of very prolonged response have been reported<sup>12</sup> but the optimal duration of targeted therapy and specifically multikinase inhibitors has not yet been fully elucidated.

These agents have different toxicities than chemotherapy and cytokines, generally of a mild/moderate degree, but some complications may be severe although manageable without serious sequelae when promptly recognized. Hypertension is a frequent side effect and has been suggested to be critical in the etiopathogenesis of some cases of cardiac toxicity<sup>13,14</sup>. Our patient has not developed overt cardiotoxicity up to now, even if hypertension management was sometimes problematic.

Patient-related factors such as low body mass, female gender and advanced age have been held responsible for the increased risk of adverse events<sup>15</sup>, and the treatment of elderly patients is controversial. The sorafenib TARGET trial did not show any difference in the clinical benefit rate for older patients<sup>16</sup> and a recent retrospective analysis of clinical trials with new agents suggests similar outcomes and toxicities in most patients over 65 years compared to younger patients<sup>17</sup>. In other reports early treatment interruptions for adverse events were not uncommon: some elderly patients can be treated successfully for a prolonged time as in our report, but the systematic application of comprehensive geriatric evaluation or multidimensional geriatric assessment may be recommendable to identify factors predicting enhanced toxicity.

In conclusion, it might be important in the treatment of older people with targeted therapies to follow these recommendations:

- assessment of the type and severity of comorbidities
- careful monitoring of cardiac, thyroid and metabolic dysfunctions
- assessment of the impact of every kind and grade of the developed toxicities on quality of life.

The optimal duration and dose of targeted therapy, especially with multikinase inhibitors, is not yet fully known, nor is the impact on response. Prolonged treatment has a higher incidence of adverse events, especially myelotoxicity as evidenced in the expanded-access trial<sup>18</sup>, but without an evident increase in serious cardiac complications.

Careful clinical monitoring of patients undergoing treatment with multikinase inhibitors with an interdisciplinary approach involving medical oncologists, urologists and other specialists is of the utmost importance to ensure adequate dose and duration of therapy in a cancer with potentially long survival. Clinical and molecular factors other than the Motzer prognostic score<sup>19</sup> have been recently identified as predictive and prognostic determinants and could be included in validated nomograms and therapeutic algorithms to guide treatment policy<sup>20,21</sup>. Identification of subjects likely to benefit from different treatment approaches and options is a priority to maximize efficacy, limit unnecessary toxicities, and hopefully preserve acceptable quality of life.

## References

1. Flanigan RC, Mickisch GH, Sylvester R, Tangel C, Van Poppel H, Crawford ED: Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. *J Urol*, 171: 1071-1076, 2004.
2. Hofmann HS, Neef H, Krohe K, Andreev P, Silber RE: Prognostic factors and survival after pulmonary resection of metastatic renal cell carcinoma. *Eur Urol*, 48: 77-81, 2005.
3. Karellas ME, Jang TL, Kagiwada MA, Kinnaman MD, Jarnagin WR, Russo P: Advanced-stage renal cell carcinoma treated by radical nephrectomy and adjacent organ or structure resection. *BJU Int*, 103: 160-164, 2008.
4. van der Poel HG, Roukema JA, Horenblas S, van Geel AN, Debruyne FM: Metastasectomy in renal cell carcinoma: a multicenter retrospective analysis. *Eur Urol*, 35: 197-203, 1999.
5. Eggener SE, Yossepowich O, Kundu S, Motzer RJ, Russo P: Risk score and metastasectomy independently impact prognosis of patients with recurrent renal cell carcinoma. *J Urol*, 180: 873-888, 2008.
6. Szczylik C, Porta C, Bracarda S, Hawkins R, Bjarnason GA, Oudard S, Lee S, Carteni G, Hariharan S, Gore ME: Sunitinib in patients with or without prior nephrectomy (Nx) in an expanded access trial of metastatic renal cell carcinoma (mRCC). *J Clin Oncol (ASCO Meeting Abstracts)*, 26: abstr 5124, 2008.
7. Pouessel D, Culine S: High frequency of intracerebral hemorrhage in metastatic renal carcinoma patients with brain metastases treated with tyrosine kinase inhibitors targeting the vascular endothelial growth factor receptor. *Eur Urol*, 2: 376-381, 2008.
8. Hariharan S, Szczylik C, Porta C, Bracarda S, Hawkins R, Bjarnason GA: Sunitinib in metastatic renal cell carcinoma (mRCC) patients (pts) with brain metastases (mets): data from an expanded access trial. *J Clin Oncol (ASCO Meeting Abstracts)*, 26: abstr 5094, 2008.
9. Medioni J, Cojocarasu O, Belcaceres JL, Halimi P, Oudard S: Complete cerebral response with sunitinib for metastatic renal cell carcinoma. *Ann Oncol*, 7: 1282-1283, 2007.
10. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD,

- Bukowski RM, Oudard S, Negrier S, Szczylik C, Pili R, Bjarnason GA, Garcia-del-Muro X, Sosman JA, Solska E, Wilding G, Thompson JA, Kim ST, Chen I, Huang X, Figlin RA: Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol*, 27: 3584-3590, 2009.
11. Heng DY, Rini BI, Garcia J, Wood L, Bukowski RM: Prolonged complete responses and near-complete responses to sunitinib in metastatic renal cell carcinoma. *Clin Genitourin Cancer*, 5: 446-451, 2007.
  12. Ronnen EA, Kondagunta GV, Ginsberg MS, Russo P, Motzer RJ: Long-term response with sunitinib for metastatic renal cell carcinoma. *Urology*, 68: 672.e19-20, 2006.
  13. Schmidinger M, Zielinski CC, Vogl U, Bojic A, Bojic M, Schukro C, Ruhsam M, Hejna M, Schmidinger H: Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol*, 26: 5204-5212, 2008.
  14. Bamias A, Lainakis G, Manios E, Manios E, Koroboki E, Karadimou A, Zakopoulos N, Dimopoulos MA: Could rigorous diagnosis and management of hypertension reduce cardiac events in patients with renal cell carcinoma treated with tyrosine kinase inhibitors? *J Clin Oncol*, 27: 2567-2569, 2009.
  15. van der Veldt AA, Boven E, Helgason HH, van Wouwe M, Berkhof J, de Gast G, Mallo H, Tillier CN, van den Eertwegh AJ, Haanen JB: Predictive factors for severe toxicity of sunitinib in unselected patients with advanced renal cell cancer. *Br J Cancer*, 99: 259-265, 2008.
  16. Eisen T, Oudard S, Szczylik C, Gravis G, Heinzer H, Middleton R, Cihon F, Anderson S, Shah S, Bukowsky R, Escudier B, for the Target Study Group: Sorafenib for older patients with renal cell cancer: subset analysis from a randomized trial. *J Natl Cancer Inst*, 15: 1454-1463, 2008.
  17. Bellmunt J, Negrier S, Escudier B, Awada A, Aapro M; SIOG Taskforce: The medical treatment of metastatic RCC in the elderly: position paper of a SIOG Taskforce. *Crit Rev Oncol Hematol*, 69: 64-72, 2009.
  18. Porta C, Szczylik C, Bracarda S, Hawkins R, Bjarnason JA, Oudard S, Lee S, Carteni G, Hariharan S, Gore ME: Short-term and long term safety with Sunitinib in an expanded access trial in metastatic renal cell carcinoma. *J Clin Oncol (ASCO Meeting Abstracts)*: abstr 5114, 2008.
  19. Motzer RJ, Bukowski RM, Figlin RA, Hutson TE, Michaelson MD, Kim ST, Baum CM, Kattan MW: Prognostic nomogram for sunitinib in patients with metastatic renal cell carcinoma. *Cancer*, 113: 1552-1558, 2008.
  20. Choueiri TK, Garcia JA, Elson P, Khasawneh M, Usman S, Golshayan AR, Baz RC, Wood L, Rini BI, Bukowski RM: Clinical factors associated with outcome in patients with metastatic clear-cell renal cell carcinoma treated with vascular endothelial growth factor-targeted therapy. *Cancer*, 110: 543-550, 2007.
  21. Choueiri TK, Vaziri SA, Jaeger E, Elson P, Wood L, Bhalla IP, Small EJ, Weinberg V, Sein N, Simko J, Golshayan AR, Sercia L, Zhou M, Waldman FM, Rini BI, Bukowski RM, Ganapathi R: von Hippel-Lindau gene status and response to vascular endothelial growth factor targeted therapy for metastatic clear cell renal cell carcinoma. *J Urol*, 180: 860-865, 2008.