Complete response to sunitinib in a patient with relapsed irresectable renal cell carcinoma

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We report a case with a complete pathology-proven remission after sunitinib treatment of a relapsed irresectable clear cell renal carcinoma. A significant objective response was observed with tumor size reduction during treatment. After surgery, on pathologic examination it was concluded that the patient exhibited a complete response; activity and the feasibility and safety of subsequent surgical resection were assessed. Otherwise after discontinuing sunitinib, the patient had a relapse on the same location; sunitinib has been resumed and was again found to be effective. ***Anti-Cancer Drugs*** **22:817–821 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Over the past few years, several drugs have shown a clear benefit for the treatment of patients with metastatic renal cell carcinoma (RCC). The most important of these are the small molecule multityrosine kinase inhibitors (TKIs), sunitinib and sorafenib, the vascular endothelial growth factor (VEGF) antibody bevacizumab and the mTOR inhibitor temsirolimus.

With the use of targeted systemic therapy, the evaluation of multimodal approaches to metastatic RCC is warranted. Integration of surgery and systemic treatment is required to optimize outcomes for patients with advanced RCC.

Sunitinib treatment has improved the overall survival and progression-free survival in metastatic RCC, and responses of the primary tumor to the therapy have also been observed. Therefore, there is increasing interest in the neoadjuvant use of targeted therapy and some studies have shown promising results [1–3].

In addition, the significant response rate to sunitinib has introduced the possibility of residual disease surgery after initial treatment with a TKI. The frequency and magnitude of tumor responses with this approach are not well defined, and surgical safety issues are of concern because of the potential impact of these agents on tissue healing and vascular integrity [4].

In this study, we present a case of complete histologic remission after sunitinib treatment of a relapsed irresectable clear cell renal carcinoma with a subsequent surgical procedure. Moreover, after discontinuing sunitinib, the patient had a relapse on the same location; showing that readministration of sunitinib was again effective.

Case report

A 64-year-old male patient was referred to the oncology department in June 2007 with diagnosis of an irresectable RCC. He had an inferior myocardial infarction in 1986.

In October 1990 (when he was 47 years) he was diagnosed with a clear cell renal carcinoma and a radical left nephrectomy was performed. Pathology showed a clear cell adenocarcinoma (pT1 G1 N0 M0) without perirenal fat and renal vein infiltration. Afterwards the patient was followed up and in December 2005, a computed tomography (CT) scan showed a 9 cm pancreatic tail mass. In February 2006, the patient underwent a pancreatectomy and splenectomy with partial resection of the colon (due to infiltration by the tumor). Pathology confirmed a renal carcinoma with pancreatic invasion.

During 2006, a CT scan showed a growing mass in the surgical field. The PET scan was positive in the retroperitoneal area and a fine needle aspiration showed clear cell carcinoma. On 17 May 2007, another laparotomy surgery was performed. An irresectable mass was observed and no procedure was performed.

The patient, now 67 years of age, was referred to our Department of Medical Oncology for treatment. A CT scan showed a 6 cm hypervascular mass (Fig. 1).

At this point, the patient was classified with good-risk Memorial Sloan-Kettering Cancer Center prognostic features [5] and was offered treatment with sunitinib. The drug was administered orally at a dose of 50 mg/day, consisting of a 4-week treatment followed by a 2-week rest period in cycles of 6 weeks. The patient started the first cycle in June 2007. After two cycles a partial

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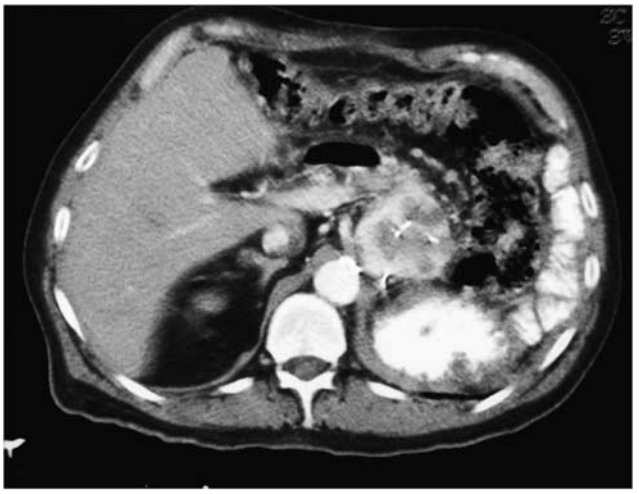
response was found on the CT scan; the mass measured 4.5×3 cm (Fig. 2). After three cycles, the patient developed grade 3 thrombocytopenia and grade 2 neutropenia and also grade 2 diarrhea and cutaneous toxicity.

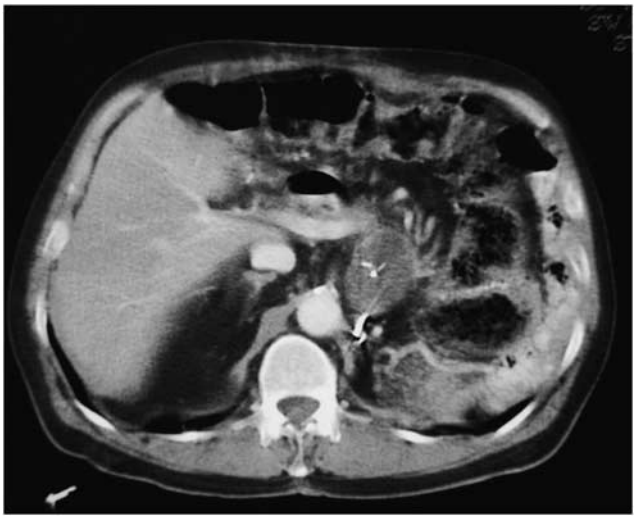
In addition, hypothyroidism was detected in a blood test. The patient was microsomal and was thyroglobulin antibody negative. A dose reduction was therefore required and from the fourth cycle onwards sunitinib was administered at a dose of 37.5 mg/day.

Fig. 1



Computed tomography scan before starting sunitinib treatment.

Fig. 2

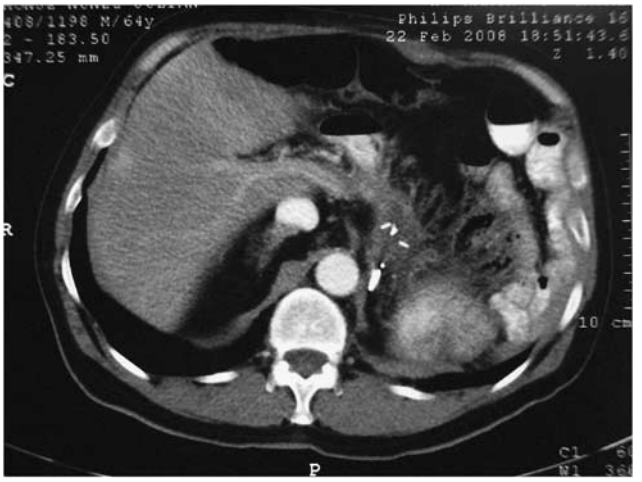


Computed tomography scan after two cycles of treatment.

CT scans showed that the lesion was becoming progressively smaller. After 11 cycles of treatment, the lesion was no longer visible on CT scan (Fig. 3). A PET scan showed a retroperitoneal lesion of 2.7×1.4 cm (Fig. 4).

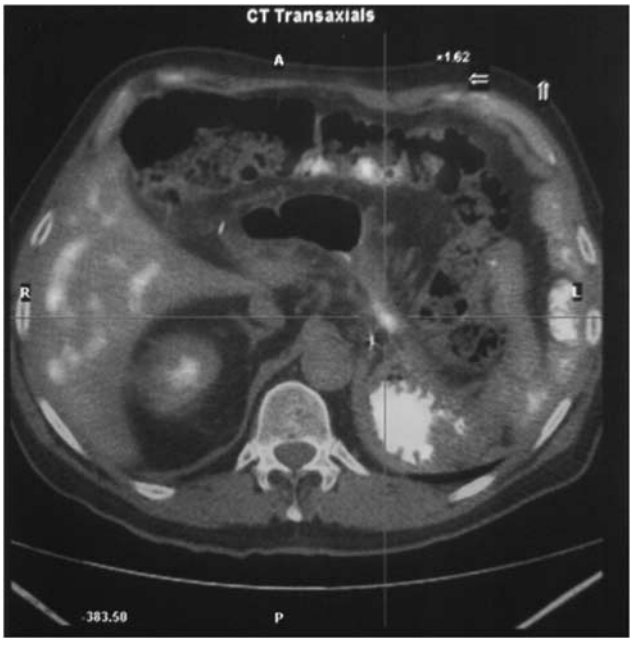
In October 2008, the patient underwent a surgical procedure and a retroperitoneal 2-cm nodule was resected. The abdominal cavity was explored and no other lesions were found. Pathology showed a fibrous tissue without malignity data. No lesions were found in a

Fig. 3



Computed tomography scan before surgery.

Fig. 4



PET scan before surgery.

postsurgical CT scan. No further treatment was proposed and the patient was regularly followed up. One year later, he had a relapse on the same location and sunitinib was restarted. Partial response was again observed in the last CT scan.

Discussion

For localized RCC, surgical resection can be curative, but for advanced RCC the prognosis is generally poor. The median survival for patients with metastatic RCC (mRCC) is 10–12 months and the 2-year survival rate is only 10–20% [5,6]. Moreover, mRCC is generally resistant to cytotoxic chemotherapy. Until recently, treatment was limited to cytokine therapies (interleukin-2 and interferon-α), as RCC evokes an immune response [7]. Interferon therapy results in responses in 10–20% of patients with a median survival of 13 months [8].

High-dose interleukin-2 results in generally durable complete responses (CRs) in approximately 6% of patients, but this treatment is associated with significant toxicity [9].

On the basis of the knowledge of the pathogenesis of RCC at the molecular level and the recent identification of specific targets, molecularly targeted therapies have been integrated into the treatment strategy for patients with advanced RCC.

Approximately 65–75% of renal epithelial tumors are of the conventional or clear cell type; the pathogenesis is well understood and has been associated with the von Hippel–Lindau (VHL) tumor suppressor gene.

In patients with VHL disease, an inherited disorder that carries an increased risk for vascular tumors, RCCs develop in 40–60% of patients. Studies have shown that sporadic (nonhereditary) clear cell RCC has genetic aspects similar to those of the VHL syndrome. Genetic analysis has shown loss of heterozygosity at the VHL locus on chromosome 3p25, and this abnormality is present in 75–80% of sporadic RCCs. In sporadic clear cell RCC tumors and patients with VHL syndrome, genetic deletions, mutations, or chemical modifications result in nonfunctional or reduced levels of the VHL gene product [10].

The VHL protein has an important role in the cellular response to hypoxia. Under conditions of normal oxygen tension, the VHL protein is bound to hypoxia-inducible factor 1α and 2α, which become ubiquitinated and are targeted for proteasomal degradation. Under hypoxic conditions (or in the absence of VHL), hypoxia-inducible factor-1α accumulates in the cell. The molecular consequence is the overproduction of growth factors such as the transforming growth factor α, platelet-derived growth factor, and VEGF, which all stimulate angiogenesis and cellular proliferation [11].

New antiangiogenic agents target these factors and have recently provided more promising treatment options. New VEGF-targeting regimens (sunitinib, sorafenib, and bevacizumab) and temsirolimus, an inhibitor of mammalian target of rapamycin kinase, have been evaluated, although they have not been directly evaluated in head-to-head trials [12].

Sunitinib is an orally bioavailable multitargeted TKI that acts on VEGF and platelet-derived growth factor receptors and on the c-Kit receptor and Fms-like tyrosine kinase-3 [13].

A phase III multicenter trial compared sunitinib with interferon-α as first-line treatments for patients with RCC and confirmed a significant increase in the objective response rate (39 vs. 8%) and median progression-free survival (11 vs. 5 months); stable disease was observed in further 40% of patients and the prolongation of overall survival with sunitinib was 26.4 vs. 21.8 months ($P = 0.051$) [1].

Adverse events included fatigue, diarrhea, hand–foot syndrome, rash, hypertension, leucopenia, and thrombocytopenia. Sunitinib has since become the first-line treatment for patients with mRCC [14,15]. Sunitinib is approved in the United States and Europe for treatment of metastatic RCC.

The utility of preoperative systemic therapy for cytoreduction has not been explored extensively because of rare objective responses to cytokine therapy and because of the anticipation that a decline in performance status with cytokine therapy would preclude a prompt transition to surgery. However, the new targeted therapies for advanced RCC, although not curative, have shown substantial improvements in response and progression-free survival for patients with metastatic disease. These compounds comprise a novel family of agents with an unprecedented ability to achieve tumor reduction in RCCs [16].

Given the partial response rate with sunitinib (and other active drugs) in mRCC, resection of residual disease after administration of initial systemic treatment could benefit some patients who could achieve a surgical CR [17–20]. CRs in patients treated with sunitinib or sorafenib have been reported but they are as rare as less than 1% [21,22]. In addition, encouraging data about the response to these treatments before surgical resection comes from studies of neoadjuvant therapy in localized tumors. This approach may enable the correlation of radiographic changes with pathological and molecular changes due to treatment and may allow the identification of response markers. Results from these studies have shown reduction of primary tumors and even some cases of complete histologic remission. In addition, a surgical technique after treatment was feasible with similar complication rates [2,3,23,24]. Currently, there is little information regarding the efficacy of this strategy.

Here we present a case of pathology-proven CR after treatment with sunitinib and after a surgical procedure. This case shows the necessity of a multimodal approach and confirms that with the advent of targeted therapy for RCC, preoperative systemic therapy presents an attractive modality for treating advanced RCCs. In some cases preoperative treatment could provide the opportunity for improvement of surgical resectability. This case also illustrates the tolerability of molecularly targeted agents, which have manageable toxicity. Cardiac toxicity has been reported, with decreased left ventricular ejection, heart failure, and myocardial ischemia or infarction. No signs or symptoms of cardiac dysfunction were observed in this patient with a history of myocardial infarction. In some studies, the overall incidence of hypertension is approximately *22%*, but no hypertension was observed in our case [25].

Thyroid dysfunction has been frequently reported in patients treated with sunitinib, and typically manifests as hypothyroidism. In an institutional series, the frequency of documented hypothyroidism was 77 and *23%* of patients needed thyroid hormone replacement [26]. In the case described here, the patient presented with hypothyroidism after two cycles, but did not have any symptoms, was self-limited with thyroid-stimulating hormone normalization during the *2* weeks off treatment and did not need any additional treatment.

The patient was troubled by diarrhea and fatigue and thrombocytopenia and neutropenia that limited the dose of sunitinib that he was able to receive. However, the majority of symptoms were controllable with dose reduction.

Moreover, many issues remain regarding the safety of preoperative treatment with antiangiogenic treatment as the angiogenesis mediated by tyrosine kinases and VEGF that is inhibited during the treatment is also an important component of the wound-healing process. There is little evidence to relate the risk of perioperative complications with concurrent multitargeted TKIs.

In the case presented here, surgery was well tolerated, even though resection was performed *2* weeks after the completion of TKI therapy (sunitinib and its active metabolite have half-lives of 40–60 and 80–100 h, respectively), and there was no apparent effect of TKI therapy on the surgical technique or its complications.

Another fact to consider is that there are no data indicating as to whether targeted drugs may be discontinued in these patients and resumed in case of recurrence of disease. The advantages of this approach are the lack of treatment-related side effects and reduced treatment-related costs.

Johannsen *et al.* [27] showed that in some of the patients analyzed, discontinuing treatment with TKIs in cases of medical and/or surgical CR may be associated with development of new lesions in addition to recurrence of the disease. Median time to progression was 6 months and readministration of TKIs was effective in all cases. However, that study had a small number of patients and a retrospective design that may introduce possible biases. Therefore, further investigation is necessary to recommend this approach. In addition, whether dose reduction instead of discontinuation is feasible for the reduction of side effects and costs of continued TKI treatment remains to be elucidated.

In the case presented here, the treatment with sunitinib was discontinued. One year later, the patient had a relapse on the same location, sunitinib was resumed and again partial response was observed, suggesting the necessity of treatment continuation after a CR to sunitinib treatment and also indicating the maintained activity after reintroduction of the treatment.

Conclusion

Antiangiogenic treatments could change strategies of care for locally advanced or metastatic RCCs, allowing surgery in some irresectable patients. Prospective trials and identification of molecular makers are necessary to show reduced recurrence and improved overall survival and to define the optimal agent and timing of therapy, quantify the risk and to identify the most appropriate treatment options.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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