

Discontinuation of the Tyrosine Kinase Inhibitor Sunitinib in Patients with Metastatic Renal Cell Carcinoma: A Case Series

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Purpose: Tyrosine kinase inhibitors (TKI) play a pivotal role in the modern treatment of patients with metastatic renal cell carcinoma (mRCC). Depending on the course and the response, the targeted therapy may last for years. Thus the question arises, if a successful treatment leading to a complete response or at least a stable disease after a partial remission, may be discontinued.

Materials and Methods: Here we present 3 patients with mRCC treated with sunitinib for at least one year, resulting in a partial response, followed by a stable disease for several years. In these patients, the treatment was interrupted for different medical reasons.

Results: After a period of 20, 33 and 34 months, respectively, the metastases of the renal cell cancer showed no signs of progression, neither clinically nor in computed tomography scans, but the side effects of TKI or the medical problem leading to treatment interruption resolved in all patients within a few weeks.

Conclusion: The discontinuation of the treatment for mRCC with TKI seems to be possible, even in those patients with a partial response only, but no complete remission has been achieved before.

Keywords: carcinoma, renal cell; kidney neoplasms; protein kinase inhibitors; drug therapy; treatment outcome; antineoplastic agents; neoplasm metastasis.

INTRODUCTION

At the time of diagnosis, 20% of all patients with renal cell carcinoma (RCC) present in a metastatic stage, resulting in a median survival of 16 months only and a five-year survival rate of less than 10%.

⁽¹⁾ This poor prognosis was mainly caused by the low efficacy of the former treatment of choice, a mixture of interferon and interleukin.⁽²⁾

Recently it has been shown that the use of multitargeted tyrosine kinase inhibitors (TKI) like sunitinib may lead to a sufficient tumor control in patients with metastatic renal cell carcinoma (mRCC). The pathophysiological base of their efficacy lies in the von Hippel-Lindau hypoxia-inducible factor and vascular endothelial growth factor (VEGF) axis that plays a central role in the development of RCC and which members work as the target of TKI.⁽³⁾ In detail, sunitinib is an orally administered TKI, that influences negatively the receptor families of VEGF and platelet-derived growth factor (PDGF) as well as FMS-like tyrosine kinase-3 receptor (flt-3) and stem cell factor receptor (c-kit). Sunitinib shows response rates of 40% in patients with mRCC, and it increases the overall survival rates to more than 2 years and the progression free survival (PFS) to about one year.⁽⁴⁾ Although in certain patients severe side effects like hypertension, leukopenia or diarrhea may occur.⁽⁵⁾ Sunitinib became one of the standard medication for the first-line treatment of patients with mRCC.

Because of its efficacy, the tumor remission reached by sunitinib or other TKI may last for years. Thus the question arises, if the medication, for example due to serious and disturbing treatment-associated complications, but also because of its high costs, can be stopped, at least in case of a complete remission.

Here we present 3 mRCC-patients with a stable disease after partial response achieved by sunitinib, in whom treatment was stopped for certain reasons. During a follow-up of 22, 34 and 33 months, respectively, no signs of significant tumor growth could be found neither clinically nor in the radiological scans performed; for this the discontinuation will be prolonged. To our knowledge this is the first report about a successful interruption of TKI-therapy in patients with persisting evidence of metastases.

MATERIALS AND METHODS

Case 1

Patient 1 is a 78-year-old woman, who underwent a left-sided nephrectomy due to a localized RCC in 1990 (the history of the three patients presented here is summarized in Table). At this time, no filiae were described. About 18 years later, in May 2008, a mass was found in the right breast, and surprisingly, the histological examination of the biopsy revealed the diagnosis of a metastasis of the RCC. Afterwards, a complete staging was performed, and further metastases involving the pancreas and both sides of the lung were detected. Because the filiae were clinically inapparent and the patient presented in a very good condition, just the conduction of controls 3 months later was recommended. Since herein a tumor progression of approximately 30% was found in September 2008, we decided to start a treatment with sunitinib by using the regular dose (50 mg/day, administered orally for 4 weeks, followed by a 2-week resting period). Due to different side effects like mucositis, constipation, headache and weakness the dosage was reduced to 37.5 mg/day for six cycles. The first controls, performed after 3 and 6 months, revealed partial responses each, while in the following computed tomography (CT) scans a stable disease was found. In October 2009, i.e. about 13 months after therapy started, the patient developed arterial hypertension, probably as a side effect of sunitinib. Although the doses of sunitinib was reduced again to 25 mg/day now and a combination of at least 6 different antihypertensive agents were used, the elevation of blood pressure persisted and became symptomatic. Thus in December 2009, 15 months after the intake of sunitinib started, we decided to stop this treatment. Within a few weeks, the blood pressure improved and the antihypertensive medication could be reduced. About four months after the use of sunitinib had been stopped, a first CT scan was performed showing no signs of tumor growth. In addition, the patient pointed out to feel much better after treatment with TKI ended and thus we agreed to continue the observational procedure. In another CT scan, performed after one year without TKI, the metastasis in the breast even became smaller spontaneously. Meanwhile the therapy with sunitinib was stopped for 33

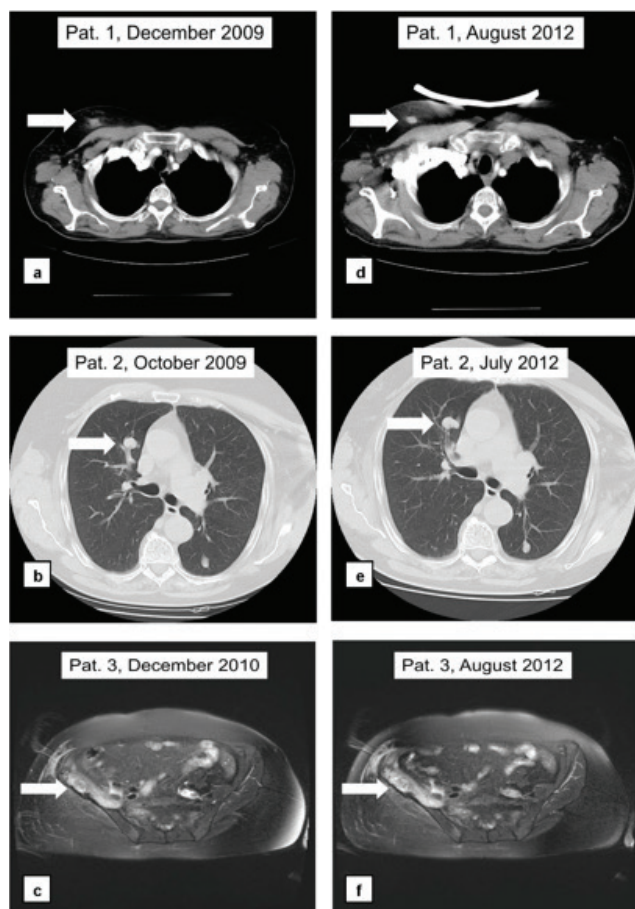


Figure. Computed tomography scans (a-d) and magnetic resonance imaging (e,f) show the exemplary course of metastases in three patients suffering from renal cell cancer. The scans at the left side were performed directly before the treatment with a TKI was stopped, the scans at the right side 32 (b), 33 (d) and 20 (f) months later.

months, however, the metastases kept stable without signs of progression (Figure, a and d).

Case 2

Patient 2 is an 87-year-old woman in a very good condition with a biological age of around 70 years. In 1996 she underwent left sided nephrectomy. Twelve years later, in June 2008, metastases in both sides of the lung and in the soft tissue of the right shoulder were detected. After confirming the diagnosis of mRCC by taking a biopsy, the lesion in the area of the right shoulder was treated for pain relief by radiotherapy till August 2008. Thereafter, in October 2008, another CT scan was performed, showing a growth-rate of the pulmonary filiae of about 20-30%; thus a systemic therapy was initiated by using sunitinib at the regular schedule

and dosage similar to the patient 1. Three weeks after treatment started, disturbing side effects like epistaxis, pain in different joints and general weakness appeared, leading to an interruption of the treatment. Within 2 weeks, the complaints vanished and the treatment could be continued, but by using sunitinib in a reduced dosage of 25 mg/day. Here-with the treatment was tolerated very well, and radiological controls performed by conventional X-rays of the lung every 3 months, revealed partial responses each. At last the pulmonary lesions nearly disappeared. However, from July 2009, the patients developed an ulcer cruris due to venous insufficiency. Although professional support by a vascular surgeon and a nurse specialized in wound care was used, the lesion did not improve; on the contrary, recurrent superinfection resulted in repeating antibiotic therapies. Therefore the patient asked for a break of the sunitinib administration, and the treatment was stopped after a 15 months period in October 2009. The controls were continued every 3 to 6 months, but even after 34 months without TKI no new filia appeared and no progression of the known metastases was found, thus, still a stable disease exists (Figure, b and e).

Case 3

In patient 3, a 60-year-old woman, a left sided nephrectomy was performed in august 2005. In November 2007 the patient developed a great metastasis with a size of 10.7-6.8 cm, including the right pelvis and the surrounding soft tissue. Since an operative approach was not possible, radiotherapy was performed from December 2007 to February 2008 (62 Gy). A CT scan in March 2008 showed a reduction of the vascular perfusion, but the size of the filia remained stable. We performed a CT scan check 12 weeks later, in which the tumor presented with little signs of growth (10-15%) and increasing vascular perfusion. Therefore, we recommended to start antineoplastic treatment with sunitinib in the regular schedule. However, due to hepatic side effects (jaundice, elevation of liver enzymes) the dosage had to be reduced stepwise to 25 mg/day, used since October 2008. In a magnetic resonance tomography of the pelvis region, performed in January 2009, the tumor size was stable, but the magnetic resonance imaging (MRI) conducted during the following months, showed changing distributions of contrast enhancement were described, and for this we as-

Table . Epidemiological data of the patients presented.

Variables	Patient 1	Patient 2	Patient 3
Sex	Female	Female	Female
Current age (years)	78	87	60
Date of first diagnosis	02/1990	06/1996	08/2005
Initial treatment	Nephrectomy	Nephrectomy	Nephrectomy
Date metastases were diagnosed	06/2008	06/2008	11/2007
Systemic treatment before TKI	No	No	No
Local treatment	No	Radiotherapy, for analgetic reason	Radiotherapy, for analgetic reason
Date TKI-treatment started	09/2008	10/2008	05/2008
Kind of TKI	Sunitinib	Sunitinib	Sunitinib
Duration of TKI-treatment (months)	15	12	30
Reason for stopping TKI	Hypertension	Superinfection, ulcerus cruris	Weakness, elevated creatinine
Progression-free survival (months) *	33	34	22

Key: TKI, tyrosine kinase inhibitor. * Still ongoing.

sumed that the malignant tissue was still vital. From March 2010 the creatinine value of the patient increased slowly, but continuously. In addition, in autumn 2010, the patient developed unspecific, but disturbing symptoms like tiredness and weakness, occurring while taking sunitinib, and for this the patient asked to stop TKI-treatment after 30 months in December 2010. Again, MRIs were performed regularly throughout the following 21 months, but neither the size nor the contrast distribution within the metastasis altered thus far (Figure, c and f).

DISCUSSION

The development of TKIs led to a fundamental change in treatment procedures of patients with mRCC, not only with regard to the good tolerance of these agents, but mainly because of their efficacy. While the median survival achieved by using cytokines did not exceed 10 months, TKI like sunitinib or sorafenib may at least double this period.^(3,6) However, as a result of the prolonged survival, numerous of the affected patients may need to take a TKI for several years, and therefore questions for example concerning the safety or the high costs of its long-term use arise. A possible answer and approach would be the controlled discontinuation of treatment, but surprisingly, beside a very few reports describing flare ups and rapid angiogenesis onset, while the use of TKI were interrupted,⁽⁷⁻⁹⁾ there are only two studies dealing with this subject.

The first study that systematically analyzed the outcome of discontinuing TKI-treatment in patients with mRCC is published by Johannsen and colleagues.⁽¹⁰⁾ The authors described 36 patients with complete remission (CR) or no evidence of disease after therapy for mRCC, in whom the treatment, mainly consisting of sunitinib, was stopped. After a median time of 7 months, the carcinoma recurred in about 65% of the patients, but about 30% of the patients remained tumor-free. In addition, Albiges and colleagues⁽¹¹⁾ described the follow-up of 36 patients with mRCC, after a CR by using a TKI (again mainly sunitinib) was achieved. While 8 of them continued treatment, 28 patients stopped taking TKI. Of these patients 61% were still disease free with a median follow-up of 8.5 months; this percentage is superior to that found by Johannsen and colleagues.⁽¹⁰⁾ By comparing these results with our limited data, some differences become obvious. At first, the treatment period in our patients took 12, 15 and 30 months with an average of 19 months, while the average treatment duration of the patients described in the studies by Johannsen and Albiges was 7.5 and 12.5 months, respectively.^(10,11) Secondly, the median follow-up of the patients mentioned in these studies was 12 and 8.5 months, respectively, but these medians consisted of a very wide range (3 to 31 months and 0.3 to 39.1 months, respectively). In opposite, the current average duration of progression free survival in our patients is 28 months, however these 3 patients were still disease-free.

Finally, the main difference between both collectives affects the outcome. Since from the results of Johannsen and colleagues⁽¹⁰⁾ a recommendation for interrupting the treatment with TKI cannot be deduced, our data as well as the results found by Albiges and colleagues⁽¹¹⁾ rather support such an approach, especially because, like Johannsen and colleagues point out, most of the patients respond to a TKI if it is re-administered in case of a progression.

Since, according to the data described above, 35 to 61% of their patients remained to be tumor-free, the authors tried to identify factors probably influencing the patient's outcome. However, neither the length of treatment before the break nor the risk profile nor the different substances used, correlate with the further course of the patients, but the authors rightly refer to the small number of patients included in the studies, which hampers reaching a significant result. Regarding our patients it is remarkable that in 2 of them the RCC relapsed after a disease-free period of more than 10 years, and all patients achieved under therapy a stable disease for a longer period. Thus it could be assumed that the tumors presented here show a reduced activity, but the histological analysis of the metastases revealed typical growth rates of 20 to 30%. However, possibly in those patients, in whom disease is stable for a longer time, either before or under treatment, the use of TKI may be stopped especially for medical reasons, but further studies are urgently needed for proofing this thesis.

CONCLUSION

We present 3 patients suffering from mRCC, in whom the treatment with the TKI sunitinib had to be stopped because of certain medical reasons. Surprisingly in all patients the tumor did not relapse to date, resulting currently in a progression free survival of at least two years. While there are 2 small studies with 72 patients in all, that deal with the interruption of TKI-treatment after achieving a CR, the successful discontinuation of sunitinib in patients, in whom just a partial response but no CR has been achieved before, is described here for the first time.

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CONFLICT OF INTEREST

None declared.

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