Kidney Cancer

Can Tyrosine Kinase Inhibitors be Discontinued in Patients with Metastatic Renal Cell Carcinoma and a Complete Response to Treatment? A Multicentre, Retrospective Analysis

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Article info

Abstract

Background: Discontinuation of treatment with tyrosine kinase inhibitors (TKIs) and readminis-tration in case of recurrence could improve quality of life (QoL) and reduce treatment costs for patients with metastatic renal cell carcinoma (mRCC) in which a complete remission (CR) is achieved by medical treatment alone or with additional resection of residual metastases.
Objective: To evaluate whether TKIs can be discontinued in these selected patients with mRCC.
Design, setting, and participants: A retrospective analysis of medical records and imaging studies was performed on all patients with mRCC treated with TKIs (n = 266) in five institutions. Patients with a CR under TKI treatment alone or with additional metastasectomy of residual disease following a partial response (PR), in which TKIs were discontinued, were included in the analysis. Outcome criteria analysed were time to recurrence of previous metastases, occurrence of new metastases, symptomatic progression, improvement of adverse events, and response to reexposure to TKIs.
Interventions: Sunitinib 50 mg/day for 4 wk on and 2 wk off, sorafenib 800 mg/day.
Measurements: Response according to Response Evaluation Criteria in Solid Tumours (RECIST).
Results and limitations: We identified 12 cases: 5 CRs with sunitinib, 1 CR with sorafenib, and 6 surgical CRs with sunitinib followed by residual metastasectomy. Side-effects subsided in all patients off treatment. At a median follow-up of 8.5 mo (range: 4–25) from TKI discontinuation, 7 of 12 patients remained without recurrence and 5 had recurrent disease, with new metastases in 3 cases. Median time to progression was 6 mo (range: 3–8). Readministration of TKI was effective in all cases. The study is limited by small numbers and retrospective design.
Conclusions: Discontinuation of TKI in patients with mRCC and CR carries the risk of progression with new metastases and potential complications. Further investigation in a larger cohort of patients is warranted before such an approach can be regarded as safe.

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1. Introduction

The prognosis of patients with metastatic renal cell carcinoma (mRCC) is poor, with a median survival duration in the range of 1 yr and a 2-yr survival rate of only 10–20% [1]. Approximately one-third of patients present with metastatic disease at the time of their initial diagnosis, and a further 25% will develop metastases at a later stage.

Sunitinib (Sutent; Pfizer, New York, NY, USA) is an orally bioavailable, small-molecule, multitargeted tyrosine kinase inhibitor (TKI) of the vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptor families as well as the Fms-like tyrosine kinase-3 (Flt-3) and stem-cell growth factor (c-KIT) receptor tyrosine kinases [2]. A large multicentre, randomised phase 3 trial compared sunitinib with interferon-alpha (IFN-α) as a first-line treatment and confirmed the high objective response rate of 39%; disease stabilisations in a further 40% of patients; a progression-free survival (PFS) of 11 mo; and recently, an overall survival (OS) of 26.4 mo [3,4]. Adverse events included fatigue, diarrhoea, hand–foot syndrome, rash, hypertension, leucopoenia, and thrombocytopoenia. Sunitinib has since become the standard of care for first-line treatment in patients with mRCC [4,5]. Approved indications for sunitinib in the United States and Europe are first-line as well as second-line treatment of mRCC.

Sorafenib (Nexavar; Bayer Schering Pharma, Berlin, Germany) is an oral, multitargeted TKI that has activity against receptors for VEGF, PDGF, Flt-3, and c-KIT. In addition, it inhibits the Raf kinases [6]. The promising results of a phase 2, placebo-controlled, randomised discontinuation study led to a phase 3, placebo-controlled, randomised trial of 905 patients who failed previous cytokine-based therapy [7]. In patients treated with sorafenib, a significant increase in PFS (5.5 mo) and OS (17.8 mo) was observed. Objective responses are seen in 10% of patients, and disease stabilisations, including minor responses, were seen in a further 74% of patients, resulting in a clinical benefit in 84% of patients receiving sorafenib. Side-effects were similar to those observed with sunitinib, with slightly less fatigue and pancytopoenia. The results of a phase 2 randomised study comparing sorafenib and interferon as a first-line treatment in patients with mRCC suggest that sorafenib is not superior to interferon in this setting [8]. Sorafenib is considered the standard second-line treatment in patients with mRCC after cytokine failure and is also approved for first-line treatment in patients in whom cytokines are not indicated or would not be tolerated [5,9].

Given the emerging role of targeted systemic therapy, reexamination of multimodal approaches to mRCC is warranted. In the era of cytokine-based therapy, consolidation of a partial remission (PR) or prolonged stabilisation by surgical resection of residual disease was a beneficial option for a relatively small proportion of patients with mRCC [10]. The significant response rate under sunitinib but also the high proportion of prolonged disease stabilisation under both sorafenib and sunitinib raise the prospect of resection of residual disease following initial administration of a TKI.

Specifically, because complete remissions with sunitinib and sorafenib are rare, patients with a PR might benefit from additional surgical resection of residual metastases, thereby achieving a surgical CR [11]. In view of the fact that continuous long-term treatment with TKIs may impair the quality of life (QoL) of a significant proportion of patients and also because of the high cost of this therapy, an intriguing question is whether TKIs can be safely discontinued in these selected patients with mRCC and resumed in case of recurrence of measurable disease. To our knowledge, there is at present no information regarding the feasibility and safety of such an approach.

2. Methods

2.1. Patients

Medical records of patients treated with TKIs for mRCC in the different institutions from November 2005 to June 2008 were reviewed. The total number of records reviewed was 266; numbers of medical records reviewed in each institution were 61, 50, 67, 25, and 63. Inclusion criteria for this analysis were (1) the absence of previously present measurable disease in imaging studies according to the Response Evaluation Criteria in Solid Tumours (RECIST), achieved either by tumournephrectomy and TKI treatment or by tumournephrectomy, TKI treatment, and additional metastasectomy; and (2) subsequent discontinuation of the TKI. Patients were classified according to the Memorial Sloan-Kettering Cancer Centre (MSKCC) risk criteria based on the following five risk factors: (1) Karnofsky performance status (PS) <80, (2) lactic dehydrogenase (LDH) >1.5 times the upper limit of normal, (3) low serum haemoglobin, (4) high corrected serum calcium >10 mg/dl, and (5) time from initial diagnosis to TKI treatment of <1 yr [12]. Some of the patients had been included in an expanded-access protocol (A6181037). In the expanded-access programme, each participant signed an institutional review board–approved, protocol-specific informed consent in accordance with national and institutional guidelines.

2.2. Treatment regimens

Sunitinib was administered orally at a dose of 50 mg/day, consisting of 4 wk on treatment followed by a 2-wk rest period

in cycles of 6 wk. Protocol A6181037 allowed continuous dosing of sunitinib at 37.5 mg/day if patients had symptoms of progressive disease during the rest period. A dose reduction to 37.5 mg, and then to 25 mg was allowed depending on the type and severity of adverse events, which were assessed according to the National Cancer Institute (NCI) common toxicity criteria (v.3.0). Sorafenib was administered orally at a dose of 800 mg daily as a continuous regimen. Dose reduction to 400 mg or 600 mg daily was allowed in case of significant adverse events.

2.3. Outcome evaluation

Outcome criteria observed after discontinuation of TKIs were time without recurrence (defined as the time between TKI discontinuation and the date of recurrent lesions on computed tomography [CT] scan), occurrence of new metastatic sites (defined as disease progression), and response to reexposure to the TKI. In addition, the improvement or disappearance of treatment-related adverse events as well as symptoms caused by tumour progression were evaluated. Tumour assessment was based on imaging with CT or magnetic resonance imaging (MRI) scans according to the RECIST criteria by one-dimensional measurement of the sum of diameters of all target lesions. Tumour response was assessed every 2–3 cycles of treatment.

3. Results

3.1. Patient characteristics

Patient characteristics are summarised in Table 1. All patients had histologically proven renal cell carcinoma (RCC) of the clear-cell subtype, with a minor component of sarcomatoid differentiation in one patient. Eleven patients received sunitinib (three as a first-line treatment, six as a second-line treatment, and two as a third-line treatment), and one patient received sorafenib (as a first-line treatment). Previous treatments and best responses are depicted in Table 1. Times on sunitinib or sorafenib before discontinuation and severe toxicities are provided in Table 2. Grade 3 toxicities were present in 6 of 12 patients. However, all patients had grade 1 and 2 side-effects, some of them significantly bothersome—in particular, fatigue and hand–foot syndrome.

Six patients reduced sunitinib dosing to 37.5 mg/day because of toxicity. Patient 3 further reduced the dose to 25 mg/day during the fourth cycle because of grade 3 hand–foot syndrome. In this patient, previous treatments with chemoimmunotherapy and sorafenib had been discontinued because of persistent, generalised skin rash and hand–foot syndrome. With sunitinib, a CR was achieved and confirmed during 6 mo at the 25 mg/day dose level before sunitinib was discontinued. The sorafenib dose in patient 12 was reduced because of grade 3 hand–foot syndrome and was subsequently kept and tolerated at 400 mg daily. A PR was achieved at 4 mo and a CR at 11 mo. Sorafenib was discontinued 6 mo later.

Table 1 – Patient characteristics

Patient	Age	Gender	Date of tumour nephrectomy	Histology of primary tumour	TNM at diagnosis	MSKCC risk group[*]	No. metastatic sites	Previous treatment(s)	Best response to previous treatment(s)
1	63	M	November 2005	Clear cell	pT3bG2NxM1	Intermediate	2	IFN/IL-2/5-FU	PD
2	65	F	September 2007	Clear cell	pT1G1NxM1	Intermediate	1[**]	–	–
3	70	F	October 2005	Clear cell	pT3bG2pN0M1	Intermediate	1	IFN/IL-2/5-FU sorafenib	SD SD
4	56	F	March 2007	Clear cell	pT3aG1NxM1	Intermediate	4	–	–
5	72	M	November 2006	Clear cell	pT3aG2N1M1	Intermediate	2	–	–
6	70	M	December 1997	Clear cell	pT1G2N0M0	Intermediate	2	IFN	PD
7	63	M	June 2005	Clear cell	pT3aG2Nx M1	Intermediate	1	Chemotherapy	SD
8	57	F	February 2006	Clear cell and sarcomatoid	pT2G3NxM1	Intermediate	2	IFN	PD
9	64	M	January 2001	Clear cell	pT1G2NxM0	Intermediate	2	IFN	PR
10	68	M	July 2003	Clear cell	pT3G2NxM1	Intermediate	3	IFN/IL-2/5-FU	PR
11	75	F	February 2002	Clear cell	PT1G1N0M0	Intermediate	3	IFN/ tumour cell vaccine	PR
12	62	F	October 2005	Clear cell	pT3G2N0M0	Intermediate	2	–	–

MSKCC = Memorial Sloan-Kettering Cancer Centre; M = male; F = female; IFN = interferon; IL-2 = interleukin-2; 5-FU = 5-fluorouracil; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease according to RECIST (Response Evaluation Criteria in Solid Tumours).

[*] Risk groups according to MSKCC criteria based on the five risk factors: low Karnofsky performance status (<80), high lactic dehydrogenase (>1.5 times the upper limit of normal), low serum haemoglobin, high corrected serum calcium (>10 mg/dl), and time from initial diagnosis to systemic treatment of <1 yr [12].

[**] Plus contralateral kidney tumour (synchronous bilateral renal cell carcinoma).

Table 2 – Data regarding tyrosine kinase inhibitor (TKI) treatment and outcome after discontinuation

Patient	Time on TKI, mo (TKI)	Dose reduction, %	Grade 3/4 toxicity[a]	Metastatic sites	Response to TKI	Sites resected surgically	Time off TKI, mo	Outcome	Action taken and result
1	19 (1)	25[b]	–	Lungs Iliac bone	PR SD	Lungs Iliac bone	6	Recurrence plus new metastases	TKI readministered (near CR)
2	6 (1)	–	–	Lungs Kidney[c]	CR PR	 Kidney	8	Disease-free	Off treatment
3	12 (1)	50	Hand–foot syndrome 3	Lungs	CR	–	3	Recurrence plus new metastases	TKI readministered (minor response)
4	7 (1)	25	–	Skin[d] Lung Adrenal	NA CR CR	Skin	5	Disease-free	 Off treatment
5	2 (1)	–	–	Lungs Lymph nodes	CR	Primary kidney tumour	8	Recurrence	TKI readministered (PR), off treatment
6	18 (1)	–	–	Liver Lymph nodes	CR CR	–	7	Recurrence	RTX mediastinum TKI readministered (minor response)
7	13 (1)	–	Neutropenia 3, trombo-cytopenia 3, fatigue 3	Liver	CR	–	25	Disease-free from RCC, but second malignancy	Off TKI treatment Radiochemotherapy for second malignancy
8	11 (1)	–	–	CNS Lungs	 PR	 Lung	11	Recurrence plus new metastases	Lung surgery TKI readministered
9	10 (1)	25	Nausea 3, Thrombo-cytopenia 3	Lungs Lymph nodes	CR	–	19	Disease-free	Off treatment
10	3 (1)	25	Fever of unknown origin 3	Lungs Lymph nodes	CR	–	7	Disease-free	Off treatment
11	5 (1)	37,5	Thrombo-cytopenia 3	Lungs[e] Thyroid[e] Pleura	NA NA CR	Lungs Thyroid	12	Disease-free	Off treatment
12	17 (2)	50	Hand–foot syndrome 3	Lungs Lymph nodes	CR	–	4	Disease-free	Off treatment

1 = sunitinib; 2 = sorafenib; CR = complete response according to Response Evaluation Criteria in Solid Tumours (RECIST); PR = partial response; SD = stable disease; NA = not applicable; RTX = radiotherapy; RCC = renal cell carcinoma; CNS = central nervous system.
[a] National Cancer Institute common toxicity criteria v.3.0.
[b] Continuous dosing as allowed per protocol A6181037.
[c] Contralateral kidney (synchronous bilateral RCC).
[d] Skin metastasis was excised before nephrectomy and sunitinib treatment.
[e] Lung metastasis was resected before interferon/vaccine treatment; thyroid metastasis was resected before sunitinib treatment.

In patient 5, cytoreductive nephrectomy was performed following administration of two cycles of sunitinib, at which time the patient had a CR of his distant metastases. Subsequently, sunitinib was withheld.

3.2. Outcome after tyrosine kinase inhibitor discontinuation

Outcomes after discontinuation of sunitinib or sorafenib are shown in Table 2. Median time off TKI in all patients was 7.5 mo (range: 3–25).

Median follow-up after discontinuation of TKI in all patients was 8.5 mo (range: 4–25).

Disease recurrencce was observed in 5 out of 12 patients, including 3 cases with new metastatic sites. Symptomatic progression occurred in one case. Median time to recurrence or progression was 6 mo (range: 3–8). Patient 1 had no signs of progression at 3 mo following discontinuation of sunitinib. At the 6-mo follow-up CT scan, a recurrence of the previous lung metastases was noted in addition to multiple new metastases in the lungs, mediastinal lymph nodes, pancreas, and soft
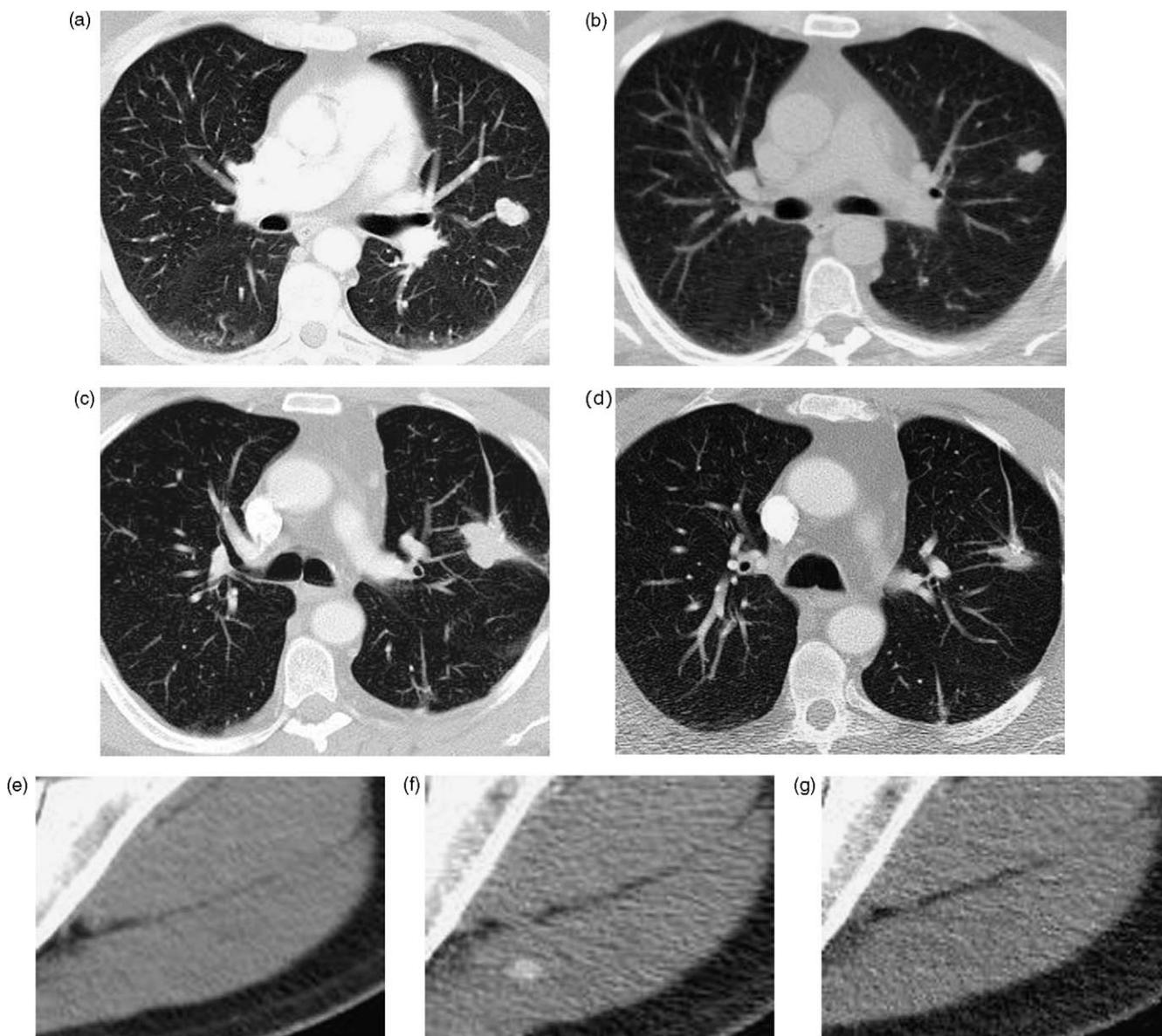
Fig. 1 – Progression of metastasis in patient 1: (a) Left pulmonary metastasis before sunitinib treatment; (b) partial remission under treatment (this lesion was subsequently resected [negative margins]); (c) new metastasis at different site 6 mo after sunitinib discontinuation; (d) partial response after retreatment with one cycle of sunitinib; (e) new soft-tissue metastasis in the gluteus muscle undetectable under treatment; (f) appearance 6 mo after discontinuation of sunitinib; and (g) complete resolution after retreatment with one cycle of sunitinib.

tissues (pectoralis and gluteus muscles). Following one cycle of sunitinib retreatment at 50 mg/day, all metastatic sites regressed almost completely (Fig. 1). In patient 3, a recurrence of one out of multiple previously known lung metastases was detected on the 3-mo follow-up CT scan along with two new metastases at a mediastinal lymph node and at the 12th thoracic vertebral body, the latter causing spinal cord compression and slight back pain but no neurologic loss (Fig. 2). In this patient, sunitinib treatment was immediately resumed at 50 mg/day; after two cycles, shrinkage of all metastases (minor response) was noted.

In patient 5, the second follow-up CT scan 8 mo after discontinuation of sunitinib demonstrated progressive disease (PD) of the small lung lesions.
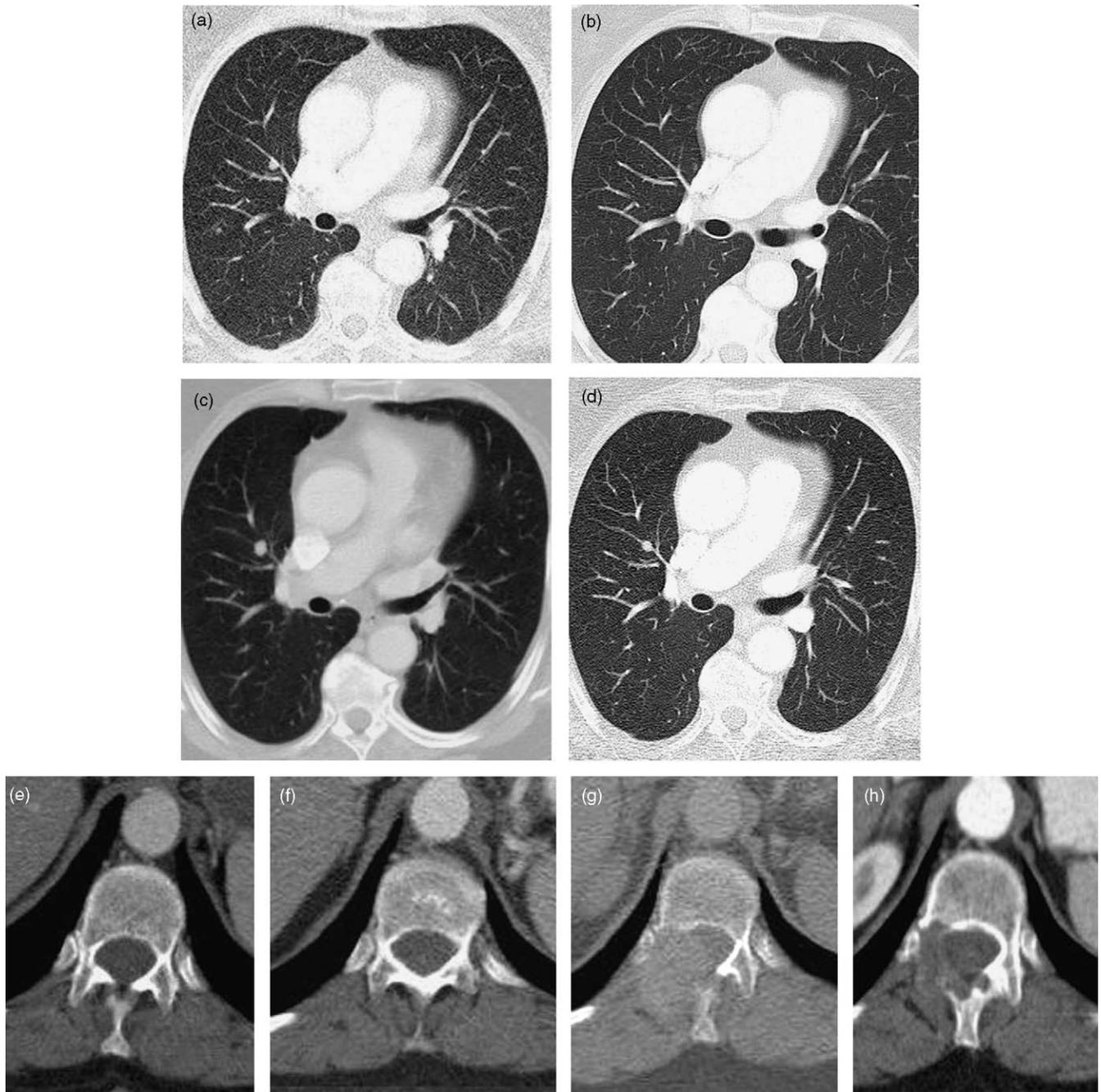
Fig. 2 – Progression of metastasis in patient 3: (a) Right pulmonary metastasis in segment 3 before sunitinib treatment; (b) resolution under treatment; (c) reappearance 3 mo after discontinuation; (d) minor response after retreatment with one cycle of sunitinib; metastasis at the 12th thoracic vertebral body, causing spinal cord compression but (e) not visible before and (f) under sunitinib treatment; (g) new appearance 3 mo after discontinuation; and (h) minor response after retreatment with one cycle of sunitinib.
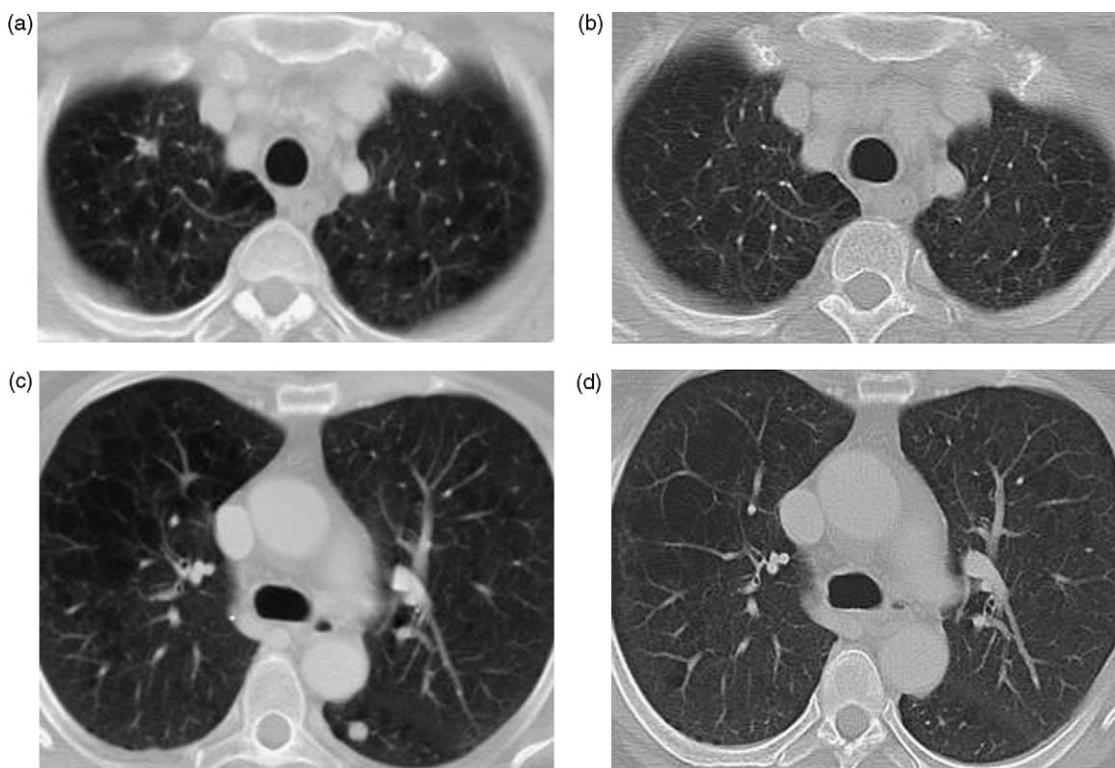
Fig. 3 – Remission of metastases in patient 12: (a) Right pulmonary metastasis before sorafenib treatment; (b) complete resolution under treatment; (c) left pulmonary metastasis before sorafenib treatment; and (d) complete resolution under treatment.

Also in this case, sunitinib treatment was readministered at 50 mg/day; after one cycle, a PR of all metastases was achieved. However, because of subjective, bothersome grade 2 fatigue, the patient wished to discontinue sunitinib again after only 1 mo of retreatment. On the follow-up CT scan 6 mo later, the patient remained stable.

Patient 6 developed recurrent thoracic lymph node metastases within 3 mo, which were treated locally by radiotherapy. Four months later, multiple lesions in the remaining kidney occurred and required additional systemic therapy with sunitinib. After the first course of therapy, a minor response was noted on CT scans. In patient 7, new cervical lymph node metastases were detected 5 mo after discontinuation of sunitinib. However, a biopsy revealed squamous carcinoma of the head and neck from a pharyngeal primary tumour that was subsequently discovered. The patient received radio-chemotherapy for this malignancy and remains without detectable recurrence from his RCC.

In patient 8, an isolated lung lesion recurred at the site of previous metastasectomy 8 mo after discontinuation of sunitinib, which was again resected surgically. Another 3 mo later, multiple small pulmonary lesions at new sites were detected,

requiring readministration of sunitinib. Response to sunitinib has not yet been determined. Patient 12, who achieved a CR with sorafenib treatment alone, remains disease-free 4 mo after discontinuation of sorafenib (Fig. 3).

4. Discussion

In contrast to previously available cytokine-based therapies for mRCC [13], treatment with the multi-kinase inhibitor sunitinib is characterised by high objective response rates and manageable toxicity. Sorafenib leads to significant tumour shrinkage in a smaller percentage of patients, but minor responses and disease stabilisations are seen in >70% of cases. However, in the majority of patients, disease palliation rather than cure is achieved with both agents [14]. An important difference compared with cytokine-based immunotherapy is the concept of continuous long-term treatment with TKIs, which is required to maintain a PR or stable disease (SD), whereas some patients treated with cytokines may remain stable for long periods of time without additional treatment. It is well documented that TKIs may be effective within weeks after initiation of

treatment but also that rapid regrowth of tumours and metastases may occur following their discontinuation. In some instances, a phenomenon of accelerated regrowth—termed *rebound phenomenon*—has been observed, which may be the result of early regrowth of the tumour vascularisation [15] or of tumoural oedema [16].

Thus, there are data to suggest that it would be unsafe to discontinue TKIs in patients who benefit from this treatment. Complete responses under sunitinib and sorafenib are rare, being on the order of <1%, but they have been reported [4,7,17]. Given the significant PR rate of sunitinib in mRCC, resection of residual disease following administration of this drug may benefit some patients who could be rendered disease-free, thereby achieving a surgical CR [11,18]. The same concept may apply to the combination of bevacizumab and interferon, which also yields significant PR rates and has recently been approved for first-line treatment of mRCC [19], and to sorafenib, despite the lower objective response rate. There are no data to indicate whether, in these selected patients, targeted drugs may be discontinued and resumed in case of recurrence of measurable disease. The aim of the present study was to analyse the feasibility and safety of such an approach.

In our cohort, 7 out of 12 of patients continue to be disease-free after discontinuation of TKIs. These patients had a significant benefit in terms of completely absent toxicity and better QoL. However, five patients had disease recurrence, and in three cases, new metastatic lesions appeared. As in patient 3, in whom a new vertebral body metastasis with spinal cord compression was detected after only 3 mo without sunitinib, these recurrences can have potentially serious complications. Although it seems likely that in this case, occurrence of this lesion may have been prevented by continuous administration of sunitinib, this conclusion remains speculative. At present, this lesion appears well controlled by reexposure to sunitinib.

Perhaps the most important notion that one may derive from our analysis is that the approach of discontinuing a TKI in case of a medical and/or surgical CR cannot be regarded as safe because three out of five patients experienced the development of new lesions in addition to recurrence of their disease. Thus, further investigation in a larger cohort of patients is warranted before such an approach can be recommended to selected patients. Whether dose reduction instead of discontinuation may be feasible to reduce side-effects and costs of continued TKI treatment and to avoid possible rebound phenomena remains to be elucidated.

Our current analysis has several important limitations. First, the small number of patients and the retrospective design incur the probability of bias. Most obvious is the disparity between medical and/or surgical CRs under sunitinib (n = 11) compared to sorafenib (n = 1) in this analysis. This disparity may, however, reflect the known higher probability of achieving an objective response under sunitinib compared to sorafenib. The sorafenib case shows that CRs are possible with this agent, which remarkably was achieved with only half of its recommended dose. No central radiologist review of all CT scans was performed. The benefit in QoL without systemic treatment, although obvious from clinical records, cannot be substantiated because of the lack of reliable assessments using appropriate questionnaires in our retrospective analysis. In addition, a cost analysis has not been performed. Finally, the short follow-up may overestimate the real proportion of patients that remain disease-free following discontinuation of the TKI. Nevertheless, given that the actual median recurrence-free interval without TKI treatment in all patients included in our study (7.5 mo) already equals the median PFS under continued treatment with some of the targeted agents available for patients with mRCC, we believe that our results are interesting and provocative.

5. Conclusions

Discontinuation of treatment and readministration in case of recurrence may be feasible for select patients with mRCC who achieve a CR under TKI treatment with or without additional metastasectomy. Advantages of this approach are the lack of treatment-related side-effects and a reduction of treatment costs. However, some patients may progress and present with new metastatic sites and potential complications. Further investigation in a larger cohort of patients is warranted before such an approach can be regarded safe.

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Editorial Comment on: Can Tyrosine Kinase Inhibitors be Discontinued in Patients with Metastatic Renal Cell Carcinoma and a Complete Response to Treatment? A Multicentre, Retrospective Analysis

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Tyrosine kinase inhibitors (TKIs) sunitinib and sorafenib are established therapies for advanced renal cell carcinoma (RCC) [1], while the combination of an anti–vascular endothelial growth factor (VEGF) monoclonal antibody, bevacizumab, has also been approved as a first-line option [2]. Although our armamentarium against this disease has been significantly enriched, there are still several questions to be answered.

In this issue of *European Urology*, Johannsen et al [3] have touched on a clinically relevant issue: the optimal duration of treatment with TKIs. They approached this question by retrospectively reviewing 12 cases of patients who achieved a complete response (CR) with TKI alone or TKI plus surgery and stopped treatment due to side effects. Some of these patients relapsed after discontinuing their treatment. The authors claim that this finding is evidence that discontinuation may not be a safe option. Nevertheless, their conclusion is not supported by this particular study, which suffers from critical limitations (some of which are acknowledged by the authors): small number of patients; retrospective rather than controlled analysis; nonuniform criteria for discontinuing treatment; TKIs used as first-, second-, or even third-line treatment. Therefore, this study cannot answer any questions but raises important ones.

Let us define the magnitude of the problem. The authors chose to study a minority of patients consisting of those with CR. Several studies have consistently shown that such patients represent <10% of cases [2,4]. Furthermore, response by Response Evaluation Criteria in Solid Tumors (RECIST) may be an inappropriate surrogate for efficacy of these agents. The question of optimal duration is important for many more patients, probably any patient with clinical benefit (ie, CR + partial response [PR] + stable disease [SD]).

In an incurable disease, the duration of therapy usually represents an equilibrium between the derived benefit and the tolerability of treatment.

All available agents for RCC have side effects, which may become serious in a minority of patients [5]. While stopping rules are clearly defined within the context of clinical studies, everyday practice requires considerable experience by the physician with the types of side effects as well as their management so that an effective treatment is not unnecessarily stopped or improperly continued. Certainly treatment discontinuation should be considered in untreatable grade 3 or 4 toxicity, and this practice should not be changed because of the observations of this report.

The relapses seen in the five patients would almost certainly have occurred even if treatment had not been discontinued. Whether they occurred earlier cannot be answered by this report. On the contrary, a more significant observation is that many of these patients responded to the reintroduction of the same agent, suggesting that temporary discontinuation of an effective agent may, in fact, be an efficient strategy because the sensitivity to this agent is retained.

In conclusion, we are far from using several effective agents in the most efficient way to treat RCC. Clinicians should continue working closely with scientists to identify molecular markers, which will aid us in individualizing therapeutic strategies and will improve on the already significant progress achieved in treating this disease.

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