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Complete Remission With Tyrosine Kinase Inhibitors in Renal Cell Carcinoma

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ABSTRACT

Purpose
Complete remission (CR) is uncommon during treatment for metastatic renal cell carcinoma (mRCC) with tyrosine kinase inhibitors (TKIs), but it may occur in some patients. It remains a matter of debate whether therapy should be continued after CR.

Methods
A multicenter, retrospective analysis of a series of patients with mRCC who obtained CR during treatment with TKIs (sunitinib or sorafenib), either alone or with local treatment (surgery, radiotherapy, or radiofrequency ablation), was performed.

Results
CR was identified in 64 patients; 36 patients had received TKI treatment alone and 28 had also received local treatment. Most patients had clear cell histology (60 of 64 patients), and all had undergone previous nephrectomy. The majority of patients were favorable or intermediate risk; however, three patients were poor risk. Most patients developed CR during sunitinib treatment (59 of 64 patients). Among the 36 patients who achieved CR with TKI alone, eight continued TKI treatment after CR, whereas 28 stopped treatment. Seventeen patients who stopped treatment (61%) are still in CR, with a median follow-up of 255 days. Among the 28 patients in CR after TKI plus local treatment, 25 patients stopped treatment, and 12 of these patients (48%) are still in CR, with a median follow-up of 322 days.

Conclusion
CR can occur after TKI treatment alone or when combined with local treatment. CR was observed at every metastatic site and in every prognostic group.

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INTRODUCTION

Before the introduction of targeted agents, cytokine therapy with interferon alfa or interleukin-2 was the standard treatment for patients with metastatic renal cell carcinoma (mRCC). Although the benefits were modest in the majority of patients, with median overall survival of approximately 13 months,[1] durable complete remissions (CRs) were achieved in some patients. Approximately 5% to 8% of patients treated with interleukin-2 achieved durable CR, which lasted for longer than 3 years.[2-4]

In recent years, targeted agents have replaced cytokine therapy as the standard of care for patients with mRCC.[5,6] Currently licensed targeted agents include the multitargeted tyrosine kinase inhibitors (TKIs) sunitinib, sorafenib, and pazopanib; the vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab in combination with interferon alfa; and the mammalian target of rapamycin kinase inhibitors temsirolimus and everolimus.[7-13]

Targeted agents have substantially improved patient outcomes, with median overall survival of more than 2 years observed with sunitinib.[7] Objective responses, mostly partial responses (PRs), are observed in approximately 8% to 39% of patients treated with targeted agents.[7-13] Although CR with targeted agents is rare, it has been observed in some patients. In the phase III study with sunitinib, CR was observed in 11 patients (3%).[7] Furthermore, several case reports and series of patients achieving CR with targeted agents, including sunitinib and sorafenib, have been published.[14-16] The characteristics of patients achieving CR during treatment with a TKI are not well defined. Furthermore, it is not yet

clear if patients achieving CR should continue targeted therapy or if it is feasible for them to discontinue treatment.

In this retrospective, multicenter study, we reviewed the medical records of patients achieving CR with the TKIs sunitinib or sorafenib, with or without additional local treatment, and analyzed the characteristics of this patient population. We also assessed whether it was feasible for patients achieving CR to stop targeted therapy and tried to define the therapeutic implications for the future.

METHODS

We performed a multicenter, retrospective analysis of patients treated for mRCC in France and one center in Switzerland, who achieved CR during treatment with a VEGF receptor TKI (sunitinib or sorafenib), either alone or in combination with local treatment (surgery, radiotherapy, or radiofrequency ablation).

A questionnaire was sent to members of the Groupe Français d'Immunothérapie asking them to identify patients with mRCC who had achieved CR after treatment with sunitinib or sorafenib, with or without additional local treatment, from November 2005 to December 2009. Patients were identified by the recollection of the treating physicians. Eligible patients were patients with histologically confirmed mRCC who had received sunitinib or sorafenib monotherapy according to the standard approved schedule and dosage. TKI therapy was only given as monotherapy. Sunitinib was administered at 50 mg daily for 4 weeks, followed by 2 weeks off treatment. Sorafenib was administered at 800 mg daily given continuously in 4-week cycles. Sunitinib and sorafenib could be prescribed in either an approved setting or as part of a clinical trial. Dose reduction for toxicity, based on the standard recommendations for the two agents, was permitted at the investigator's discretion. Patients must have achieved CR with sunitinib or sorafenib alone or in combination with a local treatment (surgery, radiation therapy, or radiofrequency ablation). CR was defined, according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as the disappearance of all known target lesions, the disappearance of all nontarget lesions, and the absence of new lesions. CR had to be confirmed on two computed tomography scans, with an interval of at least 4 weeks between scans. Each CR was reviewed and confirmed at each site as part of the process for inclusion by the medical oncologist and the radiologist in charge of urologic cancer.

The following items were recorded in the questionnaire: tumor histology, prior treatment, number and location of metastatic sites, duration of TKI treatment, nature and date of additional local procedures, and follow-up after CR. Additionally, patients were classified according to the French prognostic criteria.[17] In this classification, adverse predictive factors are performance status (PS) greater than 0, more than one metastatic site, duration of the interval between RCC diagnosis and systemic treatment of less than 1 year, and presence of liver metastases.[17] Patients were stratified as good risk (PS 0 and only one metastatic site), intermediate risk (neither good nor poor), and poor risk (PS $>$ 1 or three risk factors).[17]

RESULTS

Patient Characteristics

Sixty-four patients who experienced CR during treatment with sunitinib or sorafenib were identified in 15 centers from the Groupe Français d'Immunothérapie between November 2005 and December 2009. The majority of patients receiving sunitinib were treated outside of a clinical trial. Of the 64 patients, 36 patients had received therapy with a TKI alone, and 28 patients had received a TKI and an additional local treatment (Fig 1).

Most patients had clear cell histology (n = 60), and all patients had undergone prior nephrectomy (Table 1). The majority of patients achieving CR were at favorable or intermediate risk; however, three patients at poor prognostic risk also achieved CR. Most patients experienced CR with sunitinib treatment (n = 59); five patients had achieved CR during sorafenib treatment. Although the denominator of patients treated with sunitinib or sorafenib was not available for all centers, the incidence of CR within the main center could be defined, with a CR occurring in 1.7% of patients treated with TKIs (six of 353 patients treated with either sunitinib or sorafenib) during the enrollment period. This is in line with data from the expanded-access program with sunitinib.[18]

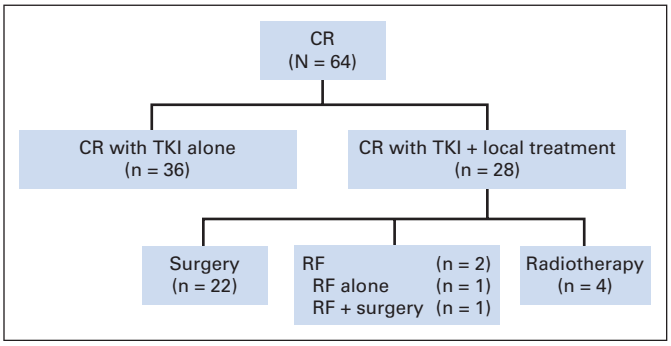

Fig 1. Achievement of complete remission (CR) with tyrosine kinase inhibitors (TKIs) alone or in combination with local treatment. RF, radiofrequency ablation.

Outcome After TKI Discontinuation

Patients achieving CR with TKI alone. Thirty-six patients achieved CR with TKI treatment alone. The median time from start of TKI therapy to CR was 12.6 months (range, 2 to 28 months). Of these,

Table 1. Patient Clinical Characteristics

Characteristic	No. of Patients	%
Treatment		
TKI alone	36	56
TKI plus local treatment	28	44
Histology		
Clear cell	60	94
Papillary	4	6
Prior nephrectomy	64	100
Prior treatment		
None	36	56
Cytokine	18	28
Local treatment: surgery/radiotherapy	8	13
Prior TKI	2	3
TKI achieving CR		
Sunitinib	59	92
Sorafenib	5	8
Prognostic group (French classification)		
Favorable	22	34
Intermediate	39	61
Poor	3	5
No. of metastatic sites before TKI		
1	26	41
2	23	36
$\geq$ 3	15	23

Abbreviations: CR, complete remission; TKI, tyrosine kinase inhibitor.

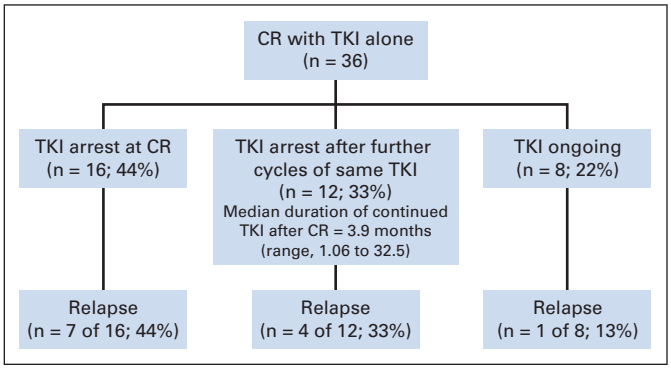

Fig 2. Outcome of patients who achieved complete remission (CR) with a tyrosine kinase inhibitor (TKI) alone.

16 patients (44%) stopped TKI treatment after CR, and 12 patients (33%) discontinued TKI treatment after further cycles of the same TKI, with a median duration of 3.9 months (range, 1.06 to 32.5 months) of TKI therapy after CR. A total of eight patients (22%) continued TKI therapy (Fig 2). Median duration of TKI therapy after CR (and still ongoing) was 10.3 months (range, 1.1 to 30.9 months).

Of the 16 patients who stopped TKI at CR, seven patients (44%) experienced relapse. Of the 12 patients who stopped TKI therapy after a further TKI period, four patients (33%) experienced relapse. One patient (13%) who continued TKI therapy also experienced disease relapse (Fig 2). Because of the small number of patients in each group, it was not possible to confirm whether there were differences in the relapse rates between patients who continued TKI therapy and those who did not. Median time from CR to relapse was 7.9 months (range, 3 to 32 months). Relapse occurred in a previously involved metastatic site in five of the 12 patients who experienced disease relapse.

Overall, of the 28 patients who stopped treatment after CR, 17 remain in CR, with a median follow-up of 8.5 months (range, 0.3 to 39.1 months). The characteristics of patients who experienced relapse versus patients who maintained a CR after cessation of TKI therapy are listed in Table 2.

Patients achieving CR with TKI and local treatment. Twenty-eight patients achieved CR after TKI therapy and local treatment. The median time from starting TKI therapy to CR was 18.5 months (range, 5 to 45 months). As such, patients received a long exposure to TKI therapy, which was then followed by an additional local treatment to enable achievement of CR. Twenty-two patients (79%) received surgery, two patients (7%) received radiofrequency ablation (one patient had radiofrequency ablation and surgery), and four patients (14%) received radiotherapy (Fig 1). The majority of patients received local treatment for pulmonary metastases; other sites of local treatment included adrenal, node, digestive tract and pancreas. Of the 22 patients who underwent surgery, pathology findings were available for 20 patients; all of the samples included residual viable tumor cells, and some samples also showed partial necrosis. Thus, none of these patients achieved a pathologic CR.

Nineteen patients stopped TKI therapy when they had achieved CR, and six patients stopped TKI therapy after further cycles of the same TKI. The median duration of the additional TKI period after CR was 3.5 months (range, 1.0 to 15.4 months). Three patients continued

Table 2. Characteristics of Patients Maintaining CR Versus Patients Experiencing Disease Relapse After Discontinuation of TKI Therapy

Characteristic	Patients Who Stopped TKI After Achieving CR With TKI Alone (n = 28)		Patients Who Stopped TKI After Achieving CR With TKI Plus Local Treatment (n = 25)	
	No. of Patients With Disease Relapse (n = 11)	No. of Patients Maintaining CR (n = 17)	No. of Patients With Disease Relapse (n = 13)	No. of Patients Maintaining CR (n = 12)
TKI treatment				
Sunitinib	9	16	13	11
Sorafenib	2	1	0	1
Median follow-up, days	480	255	688	322
Prognostic group				
Good	3	9	4	4
Intermediate	8	6	9	8
Poor	0	2	0	0
No. of metastatic sites				
1	4	9	6	5
2	6	4	5	5
3	0	3	2	1
> 3	1	1	0	1
Presence of hepatic metastases	1	4	1	0
Median time from start of treatment to CR, days	476	330	531	684
Prior treatment				
None	7	13	5	6
Cytokine	3	3	5	5
Surgery	1	1	1	0
Other	0	0	2	1
Median time until relapse, days	171	NA	270	NA

Abbreviations: CR, complete remission; NA, not applicable; TKI, tyrosine kinase inhibitor.

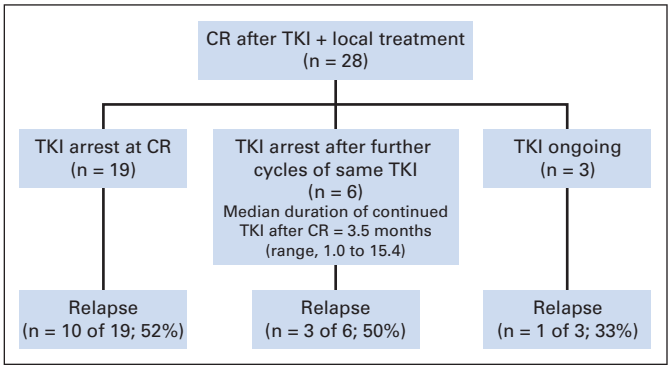

Fig 3. Outcome of patients who achieved complete remission (CR) with a tyrosine kinase inhibitor (TKI) in combination with local treatment.

to receive TKI therapy after achieving CR for a median of 8.2 months (range, 5.6 to 15.2 months; Fig 3).

Of the 19 patients who stopped TKI therapy at CR, 10 patients (52%) experienced disease relapse. Three (50%) of the six patients who stopped TKI therapy after further treatment with the same TKI also experienced relapse. Of the three patients who continued TKI therapy, one patient (33%) experienced disease relapse (Fig 3). Median time from CR to disease relapse was 8.2 months (range, 3 to 25 months). Relapse occurred in a previously involved metastatic site in nine of the 14 patients who experienced disease relapse.

Overall, of the 25 patients who stopped TKI treatment after CR, 12 patients (48%) remain in CR, with a median follow-up of 10.7 months (range, 0.3 to 54.0 months). The characteristics of patients who experienced relapse versus those who maintained a CR after cessation of TKI therapy are listed in Table 2.

Treatment of Patients Experiencing Relapse

Of the 24 patients who experienced disease relapse after discontinuation of TKI treatment, 15 patients received further systemic therapy only. Eleven patients received rechallenge with the same TKI, and four patients received another antiangiogenic treatment (three patients had an alternative TKI treatment, and one patient received bevacizumab). Patients who did not receive the same TKI at the time of disease relapse showed risk factors for resistance to the TKI, such as multiple exposures to TKI therapy and early relapse. Of the 11 patients receiving the same TKI, seven patients achieved PR, one patient had stable disease (SD), one patient had progressive disease, and the responses of two patients are unknown. Of the four patients receiving an alternative treatment, one patient had PR, two patients had SD, and one patient's response is unknown. The remaining nine patients who experienced relapse off therapy received local treatment after recurrence. Five patients had surgery, one patient had radiofrequency ablation, and three patient received radiation therapy. Of these, three patients also had rechallenge with sunitinib; all patients experienced either SD or PR.

A total of eight patients who had achieved CR with TKI therapy alone and three patients who had achieved CR with TKI therapy plus local treatment continued therapy after CR. In each of these groups, one patient experienced disease relapse. Disease relapse occurred at 10.5 and 8.2 months after CR. It should be noted that both patients had presented with multiple initial metastatic sites before the introduction to sunitinib (five sites in one patient and four sites in the other). Additionally, the relapse occurred after a CR duration of more than 8 months, and relapse for both patients was observed in only one site (cerebral). Both patients subsequently received radiotherapy; one patient additionally underwent surgery.

DISCUSSION

To our knowledge, our study is the largest series of patients with mRCC experiencing CR during TKI treatment. CR can be obtained with TKI therapy, either alone or in combination with local treatment. CR was observed during both sunitinib and sorafenib treatment. A total of 36 patients experienced CR during treatment with a TKI alone, and a further 28 patients experiencing CR had received a TKI and local treatment. With a median follow-up of 13 months from CR, 53 patients had discontinued TKI therapy, whereas 11 patients continue to receive treatment with a TKI. A total of 29 patients (55%) who discontinued treatment remain without recurrence, with a median follow-up of 8.5 months.

It is important to note that the median time between start of therapy and CR was 12.6 months in patients receiving TKI treatment alone and 18.5 months in patients receiving TKI therapy plus local treatment. This highlights the importance of maintaining therapy in patients who experience clinical benefit from TKI therapy. The difference in time to CR between the two groups may be explained by the two different treatment strategies. For example, in a patient with a good PR, treatment is often continued to assess whether a CR can be achieved. In the case of stabilization of the lesion(s) and in the absence of new lesions, a local treatment may then be considered to achieve CR. Importantly, the time to CR was within the range of previously reported case series.[19,20]

In terms of the characteristics of patients achieving CR, the majority of patients were of favorable or intermediate risk; however, three patients at poor risk were also able to achieve CR. CR also seemed to be achieved regardless of the extent of the initial disease, with patients with up to five metastatic sites achieving CR. We could not identify any clinical or biologic parameters that were associated with a patient being more likely to achieve CR. Furthermore, comparison of patients who experienced disease recurrence versus those who remained in CR did not reveal any predictive factors to aid identification of patients who would be less likely to relapse after discontinuation of therapy. Because of the small number of patients in each group, it was not possible to draw any conclusions about differences in relapse rates between patients who continued or stopped therapy.

Our results are generally consistent with those observed in previous series, which have shown that therapy with sunitinib or sorafenib, either alone or in combination with surgery, can result in CRs.[19,21] A recent retrospective series of 36 patients who discontinued targeted therapy after CR or no evidence of disease showed that 24 patients (66.7%) experienced disease recurrence after a median follow-up of 12 months after discontinuation of therapy.[21] Similar to our study, factors correlating with treatment outcome could not be identified in univariate and multivariate analyses.[21] In patients experiencing recurrence, targeted therapy was readministered in 23 patients; 18 patients received the same therapy, and five patients were switched to an alternative agent. In the patients receiving targeted therapy, one patient achieved CR, eight patients

achieved PR, and 11 patients had SD.[21] An additional study included five patients who had achieved CR; two patients achieved CR with TKI therapy alone, and three patients achieved CR with surgery (after partial remission with targeted therapy).[19] Of the patients achieving CR with TKI therapy, one patient discontinued therapy 6 months after CR, and one patient remained on therapy. The three patients who achieved CR after surgery remained on therapy for 8 to 12 months and then discontinued.[19] All patients continue to maintain CR, with a median CR duration of 24 months.[19]

In the era of cytokine-based therapy, patients achieving CR with interleukin-2 were able to maintain CR for a long period of time, without additional treatment.[2,3] However, with targeted therapy, it remains a matter of debate whether patients who achieve CR should continue or stop treatment.

It has been suggested that after CR, there may still be residual cancer cells.[19] Discontinuation of therapy may allow the cells to proliferate and lead to disease recurrence, whereas continuation of therapy maintains therapeutic pressure on the residual cancer cells, preventing disease recurrence. Furthermore, TKIs have been associated with a rebound effect, with rapid regrowth and development of metastases observed after treatment discontinuation.[22] As yet, the rebound effect has mainly been observed in preclinical models; as such, this phenomenon may not be applicable to the clinical setting. However, rare cases have been observed during the off-treatment period with sunitinib.[23,24] It has been suggested that angiogenesis inhibitors may have differing effects on primary tumors and metastases, and tumors may have an altered progression after the cessation of treatment.[25,26]

However, there are also several arguments in favor of discontinuing therapy in patients who have achieved CR. The primary reason for considering stopping therapy is toxicity. Targeted agents, such as sorafenib and sunitinib, are associated with a distinct adverse event (AE) profile.[7,8] Commonly reported AEs with sorafenib and sunitinib include fatigue, GI symptoms, and skin toxicities, such as hand-foot skin reaction and skin rash.[7,8] In a previous series of patients with CR who discontinued therapy, during the time off therapy, patients reported fewer or no AEs and felt that their quality of life was improved.[21] However, it should be noted that the majority of AEs associated with targeted agents can be effectively managed with standard medical treatments and therapy management strategies.[27,28] Finally, it has been suggested that continuation of TKI therapy during CR may lead to the development of resistance. Mechanisms of resistance associated with targeted agents are complex[29]; however, it has been hypothesized that by stopping treatment, any residual cancer cells will remain sensitive to VEGF-targeted and platelet derived growth factor–targeted therapy, whereas continuation of therapy will result in the development of resistant cancer cells.[30] The results from our study and those from previous series show that after disease recurrence, patients who had stopped targeted therapy after CR, for the most part, remained sensitive to targeted therapy, with many receiving the same TKI that had induced the initial CR. Finally, a further argument in favor of discontinuation of therapy is that stopping therapy after CR would significantly reduce treatment costs.

Our study has several limits, including the retrospective design and the selection of patients by a questionnaire, which may incur bias. Additionally, the period of follow-up is short (median follow-up, 13 months), which limits the assessment of survival of these patients. Finally, a further limitation is that there was no central radiologist review of the CRs; however, the CRs were confirmed by both the medical oncologist and the radiologist in each center.

The results from this retrospective analysis illustrate that TKIs are able to induce CRs, either alone or in combination with local treatment. Furthermore, stopping treatment with a TKI after CR may be an acceptable option. Interestingly, cessation of VEGF-targeting therapy has also recently been suggested in patients with long-term SD or toxicity, with a median time to progression of 10.0 months.[31] The clinicopathologic and biologic parameters associated with achievement of CR are not yet defined, and we could not define any predictive factors to either stop or give additional antiangiogenic drugs. As such, further research is also needed to identify factors to aid selection of patients who would be at less risk of recurrence after discontinuation of treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Final approval of manuscript: All authors

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