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REVIEW ARTICLE

Planned Discontinuation of Tyrosine Kinase Inhibitor Therapy in Metastatic Renal Cell Carcinoma: Lessons for the Era of Immunotherapy

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Abstract
Several regimens combining immunotherapy and tyrosine kinase inhibitors (TKIs) have recently been validated for the first-line treatment of patients with metastatic renal cell carcinoma (mRCC). While immunotherapy is typically discontinued after 2 years in patients who neither progress nor experience limiting toxicity, according to the protocols of most recent phase III clinical trials, TKIs are to be continued until disease progression or the emergence of limiting toxicity. However, the prolonged use of TKIs is associated with significant toxicity and financial costs. This has sparked considerable debate about whether TKIs can be safely discontinued, particularly in mRCC patients who have achieved a verified complete response. This concise review examines the available evidence on TKI discontinuation in the context of mRCC management.

Key Points

Tyrosine kinase inhibitors (TKIs) are an important part of the first-line treatment for metastatic renal cell carcinoma and are combined with immunotherapy in several novel regimens.

Although long-term treatment with TKIs is associated with substantial toxicity and costs, the criteria for stopping the treatment in good responders are unclear.

Several retrospective and prospective studies have evaluated the outcomes of planned discontinuation of TKIs in patients with renal cancer, and the strategy appears to be viable.

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1 Introduction

According to 2020 GLOBOCAN data, an estimated 430,000 people per year are diagnosed with neoplasms of the kidney, constituting 2.4% of all cancer diagnoses, excluding non-melanoma skin cancer [1]. Approximately 25–30% of these patients will present with, or will later develop, metastatic disease. Treatment for metastatic renal cell carcinoma (mRCC) has been revolutionized over the past decade due to successful clinical trials establishing immunotherapy combinations as the new standard for first-line therapy (Table 1).

These highly efficiacious therapies achieve long-term disease control in a substantial proportion of patients. It is currently a matter of controversy whether treatment can be discontinued in long-term responders, and especially in patients with verified complete response (CR). While immunotherapy was discontinued after 2 years in patients without progression or limiting toxicity in five of the six published phase III clinical trials that constitute our current base of evidence for first-line therapy of mRCC, tyrosine kinase inhibitors (TKIs) were mandated to continue beyond this point per protocol of the trials using TKI/immunotherapy combinations [2–7]. However, prolonged treatment with TKIs is associated with significant toxicities and is expensive [8].

Porta and colleagues conducted a study analyzing long-term toxicity associated with TKIs for mRCC, focusing on 807 patients who participated in clinical trials and received sunitinib for 2 years or more. During the third year of

treatment with sunitinib, the majority of these patients experienced treatment-related adverse events, including diarrhea (47%), fatigue (39%), hand-foot syndrome (31%), and hypertension (25%). Additionally, the research highlighted a cumulative risk of hypothyroidism associated with sunitinib use, which increased over time, affecting 30% of patients in the third year and 33% in the fifth year [9].

Benjamin and Rezazadeh recently assessed the costs of novel combination therapies for mRCC within the United States healthcare system. According to their analysis, TKI-related expenses account for approximately 60% of the total cost of these therapies, which reach and exceed US$500,000 for newer combinations such as lenvatinib/pembrolizumab and cabozantinib/nivolumab [10]. While some healthcare systems may be able to negotiate lower drug prices, the extremely high costs of these treatments highlights the critical need for optimizing treatment strategies. Intermittent treatment and planned discontinuation strategies are an obvious way to reduce long-term treatment toxicity and cost, provided that therapeutic efficacy is maintained. The aim of the present review is to summarize knowledge from studies exploring interruption or discontinuation of TKI monotherapy..

2 Methods

For this narrative review, publications and abstracts of retrospective and prospective studies were searched in Medline and Google Scholar using the terms “renal cell carcinoma“ (filtered for clinical trials) and “renal cell carcinoma“ in combination with the terms “treatment discontinuation“ or “intermittent treatment“. References from the identified articles were reviewed to identify further sources.

3 Retrospective Studies

Johannsen et al. undertook a retrospective analysis to explore the viability of discontinuing targeted therapy (TT) in patients with mRCC who have achieved a CR with TT alone or no evidence of disease (NED) after metastasectomy. Among the 36 patients who discontinued TT, which included agents such as sunitinib, sorafenib, bevacizumab/interferon, and temsirolimus, a recurrence of metastases was observed in 24 individuals (a recurrence rate of 67%). Re-exposure to TT proved effective in 87% of cases with recurrence. Conversely, 12 patients (33%) did not experience any recurrence during a median follow-up of 12 months. The median time off TT was 7 months. The study indicated that while a majority of mRCC patients in CR or NED do develop recurrence after stopping TT, reintroduction of therapy is largely effective, suggesting that intermittent therapy could be a potential strategy in the management of mRCC, possibly reducing exposure to the adverse effects of continuous treatment [11].

An institutional review published in 2010 analyzed 194 consecutive mRCC patients treated with sorafenib or sunitinib. Among these patients, three patients reached CR post-surgery following PR, while two attained CR after medical therapy only. At the time of the study's publication, all five patients were maintaining CR, with one still undergoing treatment and the others free from any systemic therapy, with a median CR duration of 24 months (range 24–29 months) [12].

Albiges et al. studied the phenomenon of CR achieved during TKI therapy in a multicenter retrospective analysis, examining cases where patients obtained CR under TKI therapy, either as a monotherapy or in conjunction with local treatments. Their study cohort consisted of 64 patients, predominantly exhibiting clear cell histology and having undergone previous nephrectomy. The majority of CR cases occurred during treatment with sunitinib. A significant proportion of patients who ceased treatment post-CR sustained their remission. Among the 36 patients who achieved CR with TKI alone, 28 stopped treatment. Of these, 61% were still in CR at the time of the publication, with a median follow-up of 8.5 months. Among the 28 patients in CR after TKI plus local treatment, 25 patients stopped treatment, and 12 of these patients (48%) were still in CR, with a median follow-up of 10.7 months [13].

Our collaborative group carried out a registry-based analysis to examine the prognostic outcomes for patients with mRCC who achieved CR on TT. Utilizing a national registry called RENIS, the study identified 100 patients who reached CR from a pool of 2803 patients undergoing first-line TT with anti-vascular endothelial growth factor agents such as bevacizumab, sunitinib, sorafenib, or pazopanib. With a median time to CR of 10.1 months, the median progression-free survival (PFS) after starting TT was reported at 3.8 years and the 5-year overall survival (OS) rate was 80%. An interesting aspect of the study was comparing outcomes between patients who discontinued TT within 1 month of achieving CR and those who continued TT beyond CR. The study found no significant differences in OS and PFS between the two groups, suggesting that continuation of TT post-CR may not be necessary for all patients. The patients whose disease relapsed after a treatment-free interval experienced prolonged response to retreatment [14].

Are non-CR responses achieved on TKI durable? Sadeghi et al. conducted a retrospective study of 40 patients who had stable disease (SD) or better and were taken off therapy for reasons other than disease progression. With a median follow-up of 29.7 months, the study found that 63% of the patients experienced disease progression during the

Table 1 Planned treatment duration, complete response rate, and progression-free survival in recent phase III trials of immunotherapy combinations for mRCC are key information for decision making on treatment discontinuation in patients with long-term disease control

Study	Treatment	Treatment duration		CR (%)	PFS
		Immunotherapy	TKI		
CheckMate 214 [2, 26] (patients with intermediate and poor prognosis)	Nivolumab + ipilimumab	*Ipilimumab:* Four cycles (12 weeks) *Nivolumab:* Initial protocol version – until disease progression or unacceptable toxicity; protocol amendments allowed nivolumab discontinuation after 2 years of study treatment even in the absence of disease progression or unacceptable toxicity	NA	11	PFS rates: 18 months (43%) 30 months (37%) 42 months (35%) 60 months (30%)
JAVELIN Renal 101 [4, 24]	Avelumab + axitinib	Until disease progression or unacceptable toxicity	Until disease progression or unacceptable toxicity	3.8	Median PFS 13.9 months
Keynote-426 [3, 27]	Pembrolizumab + axitinib	A maximum of 35 cycles. Patients who had a confirmed complete response could discontinue treatment after a minimum of eight cycles of treatment (approximately 24 weeks) in the pembrolizumab plus axitinib arm	Until disease progression or unacceptable toxicity	11.6	PFS rate: 18 months (48.0%) 30 months (33.0%) 36 months (29.2%) 48 months (20.9%) 60 months (18.3%)
CLEAR [6, 28]	Lenvatinib + pembrolizumab	A maximum of 35 cycles. Discontinuation of treatment considered for subjects with a confirmed CR who had been treated for at least eight cycles (at least 24 weeks) with pembrolizumab and had received at least two treatments with pembrolizumab beyond the date when the initial CR is declared	Until disease progression or unacceptable toxicity	18.3	PFS rate: 24 months (80.4%) 36 months (66.4%) 48 months (55.9%)
CheckMate 9ER [5, 29]	Cabozantinib + nivolumab	For up to 2 years	Until disease progression or unacceptable toxicity	12.4	PFS rate: 18 months (47.%) 36 months (21.0%)
COSMIC 313 [7]*	Cabozantinib + nivolumab + ipilimumab	*Ipilimumab:* Four cycles (12 weeks) *Nivolumab* for up to 2 years	Until disease progression or unacceptable toxicity	3	PFS rate 57% at 12 months

mRCC metastatic renal cell carcinoma, *TKI* tyrosine kinase inhibitor, *CR* complete response, *PFS* progression-free survival, *NA* not applicable, *COSMIC 313 enrolled only patients with intermediate or poor prognosis

treatment hiatus, with a median PFS of 10.0 months. Notably, 32% of those who progressed developed new lesions in areas previously unaffected by the disease. The study also identified independent predictors of PFS through a multivariable Cox proportional hazards model: favorable International mRCC Database Consortium risk was associated with a lower risk of progression, while achieving a CR before stopping therapy was linked to a significantly reduced risk of progression [15]. Similar results were reported by Mittal et al., who analyzed a cohort of 112 patients with at least 3-month interruption of vascular endothelial growth factor-directed treatment. The most common reason for treatment discontinuation was toxicity, but the analysis also confirmed the predictive role of CR at the time of discontinuation [16].

In a further analysis using data from the RENIS registry, we also explored the prognostic significance of different types of long-term clinical responses to TKI therapy. Using data from 219 patients, the study underscored a variance in outcomes contingent upon the best response to therapy, with complete responders exhibiting significantly elongated median PFS and OS, which were not reached, as opposed to 36.4 months and 64.9 months for partial responders (PRs), and 39.2 months and 67.9 months for patients with SD. There were no differences between the PR and SD subgroups. These results suggest that compared with patients achieving CR, patients with PR and SD do not enjoy durable disease control after responding to TKI, although survival outcomes are still excellent [17].

Several smaller studies and case reports have also suggested that discontinuation of TKI therapy is possible in carefully selected patients and may improve symptoms of toxicity without loss of response to the same targeted agent, which was usually restarted after relapse [18–20].

4 Prospective Studies

The question of planned treatment interruption was also studied in prospective trials, which largely confirmed the feasibility and safety of intermittent TKI treatment.

In a phase II, placebo-controlled, randomized trial conducted by Ratain and collaborators, planned discontinuation of sorafenib mRCC was evaluated. Initially, all participants were administered oral sorafenib. After a 12-week run-in period, patients displaying < 25% change in bidimensional tumor measurements were randomly assigned to continue with either sorafenib or a placebo. Good responders (patients exhibiting a tumor reduction of 25% or more) persisted with open-label sorafenib, whereas patients with tumor growth of 25% or greater (i.e. progressors) discontinued the treatment. Of the 65 patients with SD at 12 weeks, 32 continued with sorafenib and 33 were given a placebo. The findings at 24 weeks demonstrated a significant difference in recurrence rates: 50% of the sorafenib group remained progression-free in contrast to only 18% in the placebo group ($p = 0.0077$). Additionally, the median PFS was considerably longerin the sorafenib-treated cohort, reaching 24 weeks, compared with a mere 6 weeks in the placebo group ($p = 0.0087$). Patients experiencing disease progression while taking placebo could resume sorafenib treatment, resulting in a median interval of 24 weeks until further progression [21].

In a similar but smaller study, treatment with sunitinib was paused in patients with a 10% decrease in tumor burden, resuming when the tumor burden increased again by 10% or more. The median PFS reached 34.8 months in the 20 enrolled patients, suggesting that the strategy is feasible [22].

The largest study published as yet addressing the possibility stop-and-go therapy using TKIs in mRCC was the recently published STAR trial conducted by Brown et al. This pivotal phase II/III trial involving 920 patients tested whether temporary cessation of TKI therapy could mitigate adverse effects without compromising the therapeutic efficacy. Participants, initially treated with standard doses of sunitinib or pazopanib, were randomized to either continue therapy or to take planned treatment breaks upon achieving disease control. After a median follow-up of 58 months, the study met its non-inferiority margin for OS in the intention-to-treat (ITT) population (hazard ratio [HR] 0.97, 95% confidence interval [CI] 0.83–1.12) although not the per-protocol population, and for quality-adjusted life-years in both the ITT and per-protocol populations. Despite the median number of breaks being only one, with a median length of 87 days, the trial also highlighted the feasibility of multiple treatment interruptions. Overall, the results demonstrate the potential of employing drug-free intervals, indicating that temporary cessation of TKIs did not significantly compromise OS or quality of life [23].

Finally, TIDE-A, a prospective study presented in 2023, explored the effectiveness of the combination of avelumab and axitinib, where axitinib was stopped and avelumab continued in patients achieving PR at week 36. Treatment with axitinib was restarted in the case of progression. In this study, 79 participants were enrolled, with 29 (37%) discontinuing TKI treatment at week 36. The PFS rate after 8 weeks was 72.4%. With a median follow-up of 19.3 months, the median PFS was 23.8 months, with 70% of patients free of progression at 18 months; median OS was not reached. The average length of the treatment break was 16 weeks. As expected, patients who discontinued axitinib experienced lower treatment-related toxicity [8].

Unplanned TKI discontinuation was relatively common in immunotherapy combination trials. For trials where TKI discontinuation for adverse events has been reported separately, the rates were 12.4% for axitinib (combined with avelumab) and 16.6% and 32.0% for cabozantinib in combination with

nivolumab and ipilimumab/nivolumab, respectively [7, 24, 25]. However, the impact of this early TKI discontinuation on outcomes is unclear.

5 Conclusions

While evidence for planned treatment discontinuation of TKIs used in combination with immunotherapy for mRCC remains sparse, studies using TKI monotherapy suggest that if long-term disease control is achieved, interruption of the TKI therapy is possible. Especially for patients achieving CR, continuation of TKIs does not appear to provide any additional benefit. These findings challenge the traditional imperative of indefinite treatment for mRCC and suggest the potential for a stratified approach to TKI therapy accentuating the necessity for a more nuanced understanding of treatment cessation benchmarks. Although CR in patients treated with TKI remains a clinical rarity, its likelihood is increased when using TKI immunotherapy regimens, and it is likely that the concomitant treatment with immunotherapy would further improve the prospects of these patients. In patients not achieving CR, temporary TKI discontinuation (intermittent TKI treatment) could be well tolerated and feasible and should be further evaluated through prospective studies, several of which are ongoing (NCT04698213, NCT05219318).

Declarations

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