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Evidence and Clinical Relevance of Tumor Flare in Patients Who Discontinue Tyrosine Kinase Inhibitors for Treatment of Metastatic Renal Cell Carcinoma

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Abstract

Background: Several tyrosine kinase inhibitors (TKIs) and one monoclonal antibody targeting the vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) axis have been approved for the treatment of metastatic renal cell carcinoma (mRCC). Preclinical data suggest that cessation of anti-VEGF therapy may generate a tumor flare (TF) but its clinical relevance is still questionable.
Objective: This analysis investigates the occurrence of tumor flare and its prognostic role after discontinuation of anti-VEGFR TKIs in patients affected by mRCC.
Design, setting, and participants: Patients with mRCC treated with first-line sunitinib or pazopanib at standard dosages were screened. Patients included in the analysis were required to have: (1) discontinued treatment because of progression of disease or intolerable toxicity or sustained response; (2) evaluation of tumor growth rates immediately before (GR1) and after discontinuation (GR2); and (3) no treatment during evaluation of GR2.
Outcome measurements and statistical analysis: Overall survival (OS) was the main outcome. TF was calculated as the difference between the GR values (TF = GR2 – GR1). Cox proportional hazards regression was used to assess the prognostic role.
Results and limitations: Sixty-three consecutive patients were analyzed; the median duration of treatment was 9.3 mo, the median progression-free survival (PFS) was 11.1 mo, and the median OS was 41.5 mo. The reasons for treatment discontinuation were sustained response (partial response/stable disease) in 15.9%, toxicity in 22.2%, and progression of disease in 61.9% of cases. The median GR1 and GR2 were 0.16 cm/mo (interquartile range [IQR] –0.07 to 0.53) and 0.70 cm/mo (IQR 0.21–1.46), respectively ($p = 0.001$). In the overall population, the median TF was 0.55 cm/mo (IQR 0.08–1.22) and differed according to the reason for discontinuation: 0.15 cm/mo for response, 0.95 cm/mo for toxicity, and 1.66 cm/mo for progression. When TF was compared to other prognostic variables, Cox analysis confirmed its prognostic role (hazard ratio 1.11, 95% confidence interval 1.001–1.225; $p = 0.048$).
Conclusions: This study reports clinical evidence that TKI discontinuation results in acceleration of tumor GR and induces TF, which can negatively affect the prognosis of mRCC patients.

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Patient summary: In this report, we looked at the outcomes for patients affected by metastatic kidney tumors who discontinued treatment with antiangiogenic agents. We found that tumor regrowth after discontinuation of therapy was related to the reason for discontinuation: regrowth was higher in patients who discontinued treatment because of disease progression, and lower in patients who discontinued treatment because of a sustained response. Moreover, we found that the higher the growth rate, the shorter the survival. We conclude that discontinuation of antiangiogenic agents may cause an increase in tumor growth rate, which is related to patient survival.

1. Introduction

Renal cell carcinoma (RCC) is the sixth most common cancer diagnosis in men and the eighth most common in women in the USA, with an estimated 65 150 new cases and 13 680 deaths expected to occur in the current year [1]. In Europe, the incidence and mortality of RCC are estimated to be 71 739 and 31 293 cases per year, respectively [2,3].

The von Hippel-Lindau tumor suppressor gene has been found to be responsible for the majority of the cases of sporadic clear-cell RCC. This gene functions as a tumor suppressor, inhibiting hypoxia-inducible genes involved in angiogenesis (eg, vascular endothelial growth factor [VEGF]), cell growth, glucose uptake, and acid-base balance. Among these, VEGF and its receptor (VEGFR) are highly expressed on endothelial cells. These pathways have been found attractive as targets for molecular therapies [4].

In recent years, several tyrosine kinase inhibitors (TKIs) and one monoclonal antibody targeting the VEGF/VEGFR axis have been approved for the treatment of metastatic RCC (mRCC), based on their advantages in clinical outcomes as demonstrated in phase 3 clinical trials [5–10]. Among these, sunitinib and pazopanib are both suitable for frontline treatments and have recently been compared in a noninferiority phase 3 trial reporting similar outcomes, but different toxicity profiles [11].

These drugs have produced efficacy mainly in terms of tumor shrinkage, stabilization of disease, and delayed time to progression following a period of clinical benefit [11,12]. However, most patients will ultimately progress, suggesting a resistance to antiangiogenic agents, although approximately 25% of patients do not experience resistance because of treatment discontinuation because of adverse events [11]. Moreover, in the few patients who obtain a complete response, one of the most challenging questions is whether or not antiangiogenic treatment should be discontinued [13,14]. Preclinical data suggest that cessation of anti-VEGF therapy may accelerate tumor growth and metastatic spread [15]; this phenomenon, also called *flare-up*, has been reported in clinical practice during the off-period of sunitinib [16], but its relevance is still questionable.

The present work sought to investigate the occurrence of tumor flare and its prognostic role after discontinuation of sunitinib or pazopanib in mRCC patients.

2. Patients and methods

2.1. Patients

Patients with mRCC treated at Institut Gustave Roussy, Villejuif, France, with first-line sunitinib or pazopanib at a standard dosage were included in this study if serial computed tomography (CT) scans were available before and after treatment discontinuation. All patients discontinued treatment for progression of disease, intolerable toxicity, or sustained response, and had CT scans performed at the time of discontinuation (t_0) and before (t_{-1}) and after discontinuation (t_{+1}). In addition, eligible patients should not have received any active therapy from t_0 to t_{+1}. Reasons for the delay in the beginning of a new line of treatment included a wash-out period before inclusion in a second-line clinical trial, recovery from previous toxicity, and patient and/or physician decision.

Baseline characteristics were collected for each patient and prognosis was evaluated using International mRCC Database Consortium (IMDC) criteria [17].

2.2. Statistics

Values are expressed as median and interquartile range (IQR). The baseline was defined as the date for initiation of treatment with sunitinib or pazopanib.

We chose to evaluate the growth rate (GR) with an easy and reproducible method in clinical practice, and an Excel program for calculating this parameter is available as Supplementary File 1. For each patient, GR1 between t_{-1} and t_0, and GR2 between t_0 and t_{+1} were calculated. These values were calculated as the difference between the sum of the longest diameters (SLD) for targeted lesions evaluated by CT over time: $GR1 = SLD_0 - SLD_{-1}/t_0 - t_{-1}$ and $GR2 = SLD_{+1} - SLD_0/t_{+1} - t_0$, expressed in cm/mo. Tumor flare (TF) was defined as the difference between the GR values (TF = GR2 – GR1).

Treatment duration was calculated from the start of therapy to the time of discontinuation for any reason. Progression-free survival (PFS) was evaluated from baseline to progression of disease or death; disease progression was defined as a $\geq$20% increase in SLD according to RECIST v. 1.0 [18]. Median overall survival (OS) was evaluated for different time points: OS was evaluated from baseline to death; OS_0 was evaluated from treatment discontinuation (t_0) to death; and OS_{+1} was evaluated from t_{+1} to death. The effect of GR1 on OS_0 and of GR2 on OS_0 and OS_{+1} was evaluated. All OS values were calculated by the Kaplan-Meier method and compared across the groups using the log-rank test.

The correlation between GR or TF and other variables was evaluated using the nonparametric Spearman rank test (r_s) or the parametric Pearson test (r_p) as appropriate. Differences between groups in terms of GRs or TF were evaluated by t test.

The association of TF as a continuous variable with death (OS_0) was evaluated using the Cox proportional hazards model, and values were adjusted for IMDC criteria. All variables were considered significant at the level of $p < 0.05$. We used PASW (Predictive Analytics Software, v21; IBM

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