Original Study

Clinical Effect of Dose Escalation After Disease Progression in Patients With Metastatic Renal Cell Carcinoma

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Abstract

Patients taking tyrosine kinase inhibitors (TKIs) for metastatic renal cell carcinoma might benefit from dose escalation at the occurrence of progressive disease (PD). The data from patients who underwent TKI dose escalation at PD were retrospectively reviewed. The median duration of therapy after PD (10.1 months) was longer than that before PD (6.8 months), suggesting an antitumor effect with TKI dose escalation at PD.

Background: Given the variability in drug levels with tyrosine kinase inhibitors (TKIs) in patients with metastatic renal cell carcinoma (mRCC), dose escalation at the occurrence of progressive disease (PD) might have antitumor effects. **Patients and Methods:** The data from patients with mRCC who were treated at the Cleveland Clinic with TKIs and received a dose escalation after PD in accordance with Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1, were retrospectively reviewed. Patient- and disease-related data were collected and summarized as frequency counts and percentages or medians and ranges. The Kaplan-Meier method was used to summarize the treatment duration for the escalated doses. **Results:** Twenty-two patients were identified. Most patients (82%) were men; the median age at diagnosis was 58 years (range, 40-71 years). The most common histologic type was clear cell (73%). Axitinib was the most frequently escalated agent after PD (17 patients), followed by sunitinib (3 patients), and pazopanib (2 patients). Before PD, the median treatment duration was 6.8 months (range, 1.6-50.6 months). Of the 18 patients with evaluable tumor measurements after dose escalation, 14 (78%) had a decrease in tumor burden. The median decrease in tumor burden after dose escalation was 14% (range, 2%-58%); 4 patients (22%) had decreases $\geq$10%, 2 (11%) $\geq$20%, and 4 (22%) >30% (RECIST partial response). At the last follow-up examination, 5 patients (23%) continued to be treated at escalated doses. The median duration of escalated therapy was estimated at 10.1 months (range, 0.6 to 37.9 months). **Conclusion:** Dose escalation of TKIs after PD for select patients with mRCC can lead to a reduction in tumor burden and extend the duration of therapy.

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Introduction

Angiogenesis is a primary mechanism of tumor growth in renal cell carcinoma (RCC), and drugs that target angiogenesis along the vascular endothelial growth factor (VEGF) pathway are a cornerstone of therapy for metastatic RCC (mRCC).[1-4] However, drug level variability among patients treated with VEGF receptor (VEGFR) tyrosine kinase inhibitors (TKIs) presents a significant challenge in the treatment of patients with mRCC. At a given dose, the plasma exposure varies and correlation is lacking between the plasma levels and efficacy in individual patients.[5,6] The pharmacokinetics of TKIs have demonstrated significant interindividual variability, which might contribute to the variable clinical response in patients.[7]

The variability in plasma exposure and clinical efficacy is reflected in the dosing recommendations for these TKIs. These small molecule drugs were developed with dosing schedules and titration strategies to account for interpatient variability and

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toxicity and to achieve optimal outcomes.[6,8] However, current dose titration schemes remain imperfect, and a subset of patients will remain with subtherapeutic drug levels.[6] It can, therefore, be hypothesized that progressive disease (PD) during VEGFR TKI therapy might not be a product of resistance to therapy but rather a result of underdosing and a lower than necessary plasma level to achieve or sustain a response. Patients might thus require TKI dose escalation at the occurrence of PD to achieve optimal benefit from therapy. The goal of the present analysis was to investigate the tolerability and clinical effect of TKI dose escalation after PD.

Patients and Methods

We conducted a retrospective review of patients with mRCC treated with TKIs at the Cleveland Clinic and identified those patients who, at investigator-assessed PD as defined by Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1, underwent subsequent TKI dose escalation.[9] The patient- and disease-related characteristics were retrospectively collected from the electronic medical records. The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria were used to determine the patient prognostic groups.[10] Patient- and disease-related data were collected and summarized as frequency counts and percentages or medians and ranges. The Kaplan-Meier method was used to summarize the treatment duration for the escalated doses.

Table 1 Patient Characteristics

Factor	n (%) or Median (Range)
Gender	
Male	18 (82)
Female	4 (18)
Age at diagnosis (years)	58 (40-71)
Histologic type	
Clear cell	16 (73)
Papillary	3 (14)
Clear cell + papillary	2 (9)
Unclassified	1 (5)
Metastatic disease sites at diagnosis	
Lung	15 (68)
Lymph nodes	11 (50)
Liver	4 (18)
Adrenal glands	3 (14)
Bone	2 (9)
Other	7 (32)[a]
KPS at baseline of escalated TKI[b]	
100	2 (9)
90	10 (45)
80	8 (36)
IMDC risk group[b]	
Favorable	3 (14)
Intermediate	17 (77)
Unfavorable	1 (5)

Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; KPS = Karnofsky performance status; TKI = tyrosine kinase inhibitor.
[a]Contralateral kidney in 2 and peripancreatic/perihepatic, pleura, peritoneum peripancreatic/perihepatic plus chest wall, and pancreatic metastases in 1 patient each.
[b]Data missing for 2 patients.

Table 2 Before Therapy and Response to Dose Escalation

Factor	n (%) or Median (Range)
Dose-escalated treatment	
Axitinib	17 (77)
Sunitinib	3 (14)
Pazopanib	2 (9)
Treatment "line" escalated	
1	7 (32)
2	6 (27)
3	6 (27)
4	2 (9)
6	1 (5)
Initial treatment duration (mo)	6.8 (1.6-50.6)
Best response before dose escalation	
PR	8 (36)
SD	14 (64)
Escalated treatment duration (mo)[a]	10.15 (0.6-37.9)
Best response after dose escalation[b]	
PD	1 (6)
SD	13 (72)
PR	4 (22)
Patients with decreased tumor burden[b] (%)	14 (78)
<10	4 (22)
≥10	4 (22)
≥20	2 (11)
≥30	4 (22)
Reason for discontinuation of therapy[c]	
Disease progression	10 (45)
Toxicity[d]	4 (18)
Other[e]	3 (14)

Abbreviations: PD = progressive disease; PR = partial response; SD = stable disease.
[a]Kaplan-Meier estimate of the median.
[b]A total of 18 evaluable patients.
[c]A total of 17 patients had discontinued therapy at the time of analysis.
[d]One patient each experienced diarrhea, fatigue, palmar-plantar erythrodysesthesia; 1 patient experienced combined fatigue, diarrhea, and weight loss.
[e]One patient each was lost to follow-up, experienced cancer-related pain, or was admitted to the hospital for a non–drug-related cause.

Results

Patient Characteristics and Previous Therapies

A total of 22 patients with mRCC who underwent dose escalation of VEGFR TKIs from May 2012 to August 2015 were identified (Table 1). Most patients (82%) were men; the median age at diagnosis was 58 years (range, 40-71 years). Of the 22 patients, 16 (73%) had pure clear cell histologic features, with all but 1 patient having undergone previous nephrectomy. Seventeen patients (77%) had intermediate-risk disease using the IMDC criteria. All patients had a Karnofsky performance status