Absence of Significant Correlation of Adverse Events Between First- and Second-Line Tyrosine Kinase Inhibitors in Patients With Metastatic Renal Cell Carcinoma

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Abstract

Several adverse events (AEs) are known to be commonly observed during treatment with different tyrosine kinase inhibitors (TKIs) in patients with metastatic renal cell carcinoma (mRCC) patients. However, no significant correlation appears present in the profiles of such AEs between first- and second-line TKI therapies. Therefore, a second-line targeted agent for patients with mRCC could be selected irrespective of the AE profile during first-line TKI therapy.

Background: Several adverse events (AEs) commonly observed during treatment with different tyrosine kinase inhibitors (TKIs). The objective of the present study was to investigate whether the appearance of such AEs during treatment with first-line TKIs significantly affects the occurrence of AEs during second-line TKI therapy for patients with metastatic renal cell carcinoma (mRCC). **Patients and Methods:** The present study included 154 consecutive patients with mRCC treated with second-line TKIs after the discontinuation of first-line TKIs. The association of AEs, including diarrhea, fatigue, hand-foot syndrome, hypertension, and hypothyroidism, between first- and second-line therapies was analyzed in these 154 patients. **Results:** For all 5 AEs assessed in the present study, the proportion of patients experiencing AEs or those grade $\geq$ 3 during second-line TKI therapy was not significantly different among the following 3 groups: patients without AEs, those with grade $\leq$ 2 AEs, and those with grade $\geq$ 3 AEs during first-line TKI therapy. Furthermore, no significant difference was seen in progression-free or overall survival after the introduction of second-line TKIs between patients with and without grade $\geq$ 3 AEs during treatment with first-line TKIs. **Conclusion:** The incidence of AEs or grade $\geq$ 3 AEs during second-line TKI therapy are not dependent on the profiles of AEs during first-line TKI therapy in patients with mRCC. Therefore, AEs that occur during first-line TKI therapy should not affect the selection of second-line targeted agents for patients with mRCC.

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Introduction

Until recently, immunotherapy using cytokines had been the mainstay of systemic therapy for patients with metastatic renal cell carcinoma (mRCC). However, this treatment could provide only limited efficacy, with a median overall survival (OS) of approximately 1 year.[1] To overcome the poor prognostic outcomes of patients with mRCC, novel molecular-targeted agents have been developed by intensive investigation of the molecular mechanisms mediating the progression of RCC. The recent introduction of these agents into clinical practice has resulted in a marked paradigm shift in the therapeutic strategy for mRCC.[2]

Of the several types of molecular-targeted agents, tyrosine kinase inhibitors (TKIs), which have been shown to mainly inactivate vascular endothelial growth factor (VEGF)-related pathways, are regarded as exerting powerful antitumor activities against mRCC according to the findings of pivotal randomized clinical trials.[3-6] Therefore, TKIs currently play crucial roles in the treatment of patients with mRCC, in particular, as a first-line standard of care.[7,8] Moreover, the favorable clinical outcomes on the use of TKIs against mRCC were confirmed in various studies evaluating these

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agents in routine clinical settings.[9-13] However, limited data are available with respect to sequencing therapy to determine the most effective second-line agent after the discontinuation of first-line TKIs, particularly for patients experiencing intolerable adverse events (AEs).

It has been well-recognized that several common AEs are frequently observed during the treatment of mRCC patients with different TKIs.[3-6,9-15] Accordingly, it has become a commonly held belief that patients who stop receiving first-line TKIs because of severe AEs should switch to an alternative agent with a mechanism of action different from that of TKIs to avoid the occurrence of AEs similar to those observed during first-line TKI therapy. However, this practice has not been based on reliable data with a high evidence level. Considering these findings, we retrospectively assessed the clinical outcomes of 154 consecutive patients with mRCC who had received second-line TKI therapy after the discontinuation of first-line TKI therapy. Our study focused on the association of AE profiles between the first- and second-line agents.

Patients and Methods

We retrospectively reviewed the data from all patients with mRCC treated with molecular-targeted agents in a routine clinical setting at our institutions from April 2008 to December 2014. Of these, the present study included of 154 consecutive patients with mRCC who had received TKIs as first-line molecular-targeted agents and subsequently received a TKI different from that used as the first-line agent as second-line targeted therapy. Of the 154 patients, 9, who had not undergone radical nephrectomy, underwent needle biopsies of either the primary or the metastatic tumor to determine the histologic subtype. Therefore, all the included patients had a pathologic diagnosis of RCC. Each patient provided informed consent before participating in the present study, and the research ethics committee of our institution approved the study design.

In the present series, immunotherapy using interferon-alfa and/or interleukin-2 was the only systemic therapy allowed before the introduction of first-line TKIs. TKIs were administered according to the following schedules: sorafenib, 400 mg orally, twice daily; sunitinib, 50 mg orally, once daily in repeated 6-week cycles consisting of 4 weeks on therapy, followed by 2 weeks off; and axitinib, 5 mg orally, twice daily. The administration of TKIs was continued until disease progression or intolerable AEs developed. As a rule, dose modification of TKIs was considered for patients with treatment-associated AEs corresponding to grade ≥ 3 as follows. For sorafenib, the dose was reduced from 800 to 400 mg once daily, followed by an additional dose reduction to a single 400-mg dose every other day. For sunitinib, the initial dose reduction was from 50 to 37.5 mg once daily, and then to 25 mg once daily. For axitinib, an increased dose of 7 mg twice daily was allowed for patients who had tolerated the standard dose for ≥ 2 weeks, unless the blood pressure was $>$ 150/90 mm Hg or they were taking antihypertensive medication, and the dose was reduced to 3 mg twice daily and then further to 2 mg twice daily.

As baseline evaluations, the clinicopathologic examinations and performance status were assessed using the International Union Against Cancer TNM classification system and Karnofsky performance status scale, respectively. Risk classification was conducted using both the Memorial Sloan Kettering Cancer Center and Heng's risk classification systems.[16,17] Before the initiation of TKI treatment, radiologic evaluations were performed for all patients by computed tomography of the brain, chest, and abdomen and radionuclide bone scanning. Tumor measurements were conducted by computed tomography before and every 12 weeks after the introduction of TKIs. Treatment responses and AEs were evaluated by the treating physician using the Response Evaluation Criteria in Solid Tumors, version 1.1, and the National Cancer Institute

Table 1 Patient Characteristics at Treatment Initiation of TKIs

Characteristic	Value
Age (year)	
Median	61
Range	37-86
Gender	
Male	119 (77.3)
Female	35 (22.7)
Previous nephrectomy	
Yes	144 (93.5)
No	9 (6.5)
Previous immunotherapy	
Yes	37 (24.0)
No	117 (76.0)
MSKCC risk classification	
Favorable	54 (35.1)
Intermediate	84 (54.5)
Poor	16 (10.4)
Heng risk classification	
Favorable	46 (29.9)
Intermediate	93 (60.4)
Poor	15 (9.7)
C-reactive protein	
<0.8 mg/dL	105 (68.2)
≥0.8 mg/dL	49 (31.8)
Metastatic organ	
Lung	98 (63.6)
Lymph node	33 (21.4)
Bone liver	16 (10.4)
Brain	8 (5.2)
No. of metastatic organs	
1	82 (53.2)
2	62 (40.3)
>3	10 (6.5)
Histologic subtype	
Clear cell carcinoma	139 (90.3)
Other	15 (9.7)
Sarcomatoid features	
Yes	15 (9.7)
No	139 (90.3)

Data presented as n (%), unless otherwise noted.
Abbreviations: MSKCC = Memorial Sloan Kettering Cancer Center; TKIs = tyrosine kinase inhibitors.