Promising response to axitinib rechallenge for metastatic renal cell carcinoma after progression on prior axitinib: report of two cases

Hideaki Miyake^{1,2} · Ken-ichi Harada¹ · Masato Fujisawa¹

Received: 7 July 2017 / Accepted: 2 November 2017 / Published online: 14 November 2017
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Abstract

With the marked improvement in the prognosis of patients with metastatic renal cell carcinoma (mRCC) in the era of molecularly targeted therapy, sequential therapies using multiple targeted agents have been intensively performed for these patients. Despite being conducted targeting small cohorts, several studies showed efficacious findings on rechallenge with some targeted agents, such as sunitinib and sorafenib; however, there has not been any report describing axitinib rechallenge for patients with mRCC. Here, we report two cases of mRCC showing a significant response to axitinib rechallenge after progression on prior systemic treatment with multiple agents, including axitinib. These findings suggest that mRCC, once refractory to axitinib, can still show favorable disease control on rechallenge with this agent during sequential treatment with targeted agents.

Keywords Metastatic renal cell carcinoma · Rechallenge · Axitinib

Introduction

Over the past decade, various types of novel agents targeted against signaling transduction pathways mediating the progression of renal cell carcinoma (RCC) have been introduced into clinical practice, resulting in the marked improvement in the prognosis of patients with metastatic RCC (mRCC) [1]. Of these agents, anti-vascular endothelial growth factor (VEGF) receptor–tyrosine kinase inhibitors (TKIs) are regarded as exhibiting powerful antitumor activities against mRCC based on the outcomes of pivotal randomized clinical trials; thus, TKIs currently play central roles in the treatment of patients with mRCC [1–4]. However, resistance to TKIs eventually develops in the majority of mRCC patients, indicating that these patients receive sequential therapies with multiple targeted agents to further maintain disease control [5].

To date, several studies have demonstrated the absence of a correlation of therapeutic efficacy among TKIs sequentially administered to mRCC patients [6–8]. For example, Escudier et al. reported no significant difference in the median PFS with second-line axitinib for mRCC patients with disease that responded or did not to the first-line sunitinib [6]. Furthermore, despite being assessed in small cohorts or case reports, rechallenge with TKIs, such as sunitinib and sorafenib, has been shown to have a potential benefit in selected mRCC patients [9–12]. Collectively, these findings suggest that axitinib, one of the standard agents for mRCC patients after failure of first-line systemic therapy [1, 4], may be expected to have a significant value for treating mRCC in a rechallenge setting; however, there has not been any study examining the usefulness of axitinib rechallenge for patients with mRCC. In this report, we describe two patients with mRCC who showed a response to axitinib after being refractory to prior treatment with axitinib.

✉ Hideaki Miyake
hideakimiyake@hotmail.com

¹ Division of Urology, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

² Department of Urology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-Ku, Hamamatsu 431-3192, Japan

Case report

Case 1 was a 57-year-old woman, who was diagnosed with left RCC accompanying multiple lung metastases, underwent left radical nephrectomy in June 2004, and the pathological diagnosis of the resected specimen was clear cell carcinoma,

pT3a, and Fuhrman grade 3. After surgery, interferon- α (IFN- α) therapy was initiated for the treatment of lung metastases in this patient. As shown in Table 1, she subsequently received low-dose interleukin-2 (IL-2), sunitinib, axitinib, and temsirolimus as the second-, third-, fourth-, and fifth-line therapies, respectively. During the fifth-line therapy, liver metastases were newly developed, and as sixth-line therapy, rechallenge with axitinib was performed in May 2015 when she was classified into an intermediate-risk group based on the Memorial Sloan-Kettering Cancer Center (MSKCC) system for previously treated mRCC patients [13]. Although the response to prior treatment with axitinib was judged to be stable disease (SD) and progressive disease developed 10 months after the introduction of this agent, the significant regression of metastatic lesions in the lung and liver was observed on axitinib rechallenge (Fig. 1), and its therapeutic effect was a partial response (PR), which was maintained for 8 months. As adverse events (AEs) during treatment with axitinib, diarrhea (grade 2), hypertension (grade 2), and dysphonia (grade 1) were developed at both fourth- and sixth-line therapies. After becoming refractory to axitinib rechallenge, she currently receives pazopanib as the seventh-line systemic therapy.

Case 2 was a 69-year-old man with clinically localized right RCC, who underwent right radical nephrectomy in June 2003. Pathological examination revealed that the resected tumor was pT3a and Fuhrman grade 3. Two years after surgery, multiple lung metastases developed, and he received combined treatment with IFN- α and low-dose IL-2. Thereafter, sorafenib, sunitinib, axitinib, and temsirolimus were administered to this patient as the second-, third-, fourth-, and fifth-line therapies, respectively. In June 2015, he then received rechallenge with axitinib as sixth-line therapy, and at that time, he was judged to be an intermediate-risk group [13]. The response to prior axitinib was SD, and progression occurred 19 months after treatment with this agent; however, PR was achieved by rechallenge with axitinib as the sixth-line therapy, showing the significant improvement of lung metastatic lesions, pleural effusion, and atelectasis (Fig. 2). These effects have persisted for 12 months to date. As AEs associated with the use of axitinib, only diarrhea (grade 2) was observed at fourth-line therapy, while proteinuria (grade 1) and fatigue (grade 1) in addition to diarrhea (grade 2) occurred at the sixth-line therapy.

Discussion

Due to the introduction of various types of efficacious molecularly targeted agents, particularly that of TKIs, intensive sequential therapy using multiple targeted agents has been widely performed for mRCC patients, resulting in the significant improvement of the prognosis of these patients [1,

Table 1 Summary of sequential therapy for two patients undergoing axitinib rechallenge

Case	First line			Second line			Third line			Fourth line			Fifth line			Sixth line		
	Agent	Duration (months)	Response ^a	Agent	Duration (months)	Response ^a	Agent	Duration (months)	Response ^a	Agent	Duration (months)	Response ^a	Agent	Duration (months)	Response ^a	Agent	Duration (months)	Response ^a
1	IFN- α	25	SD	IL-2	26	SD	Suni	66	SD	Axi	10	SD	Tern	7	SD	Axi	8	PR
2	IFN- α /IL-2	31	PR	Sora	25	SD	Suni	27	SD	Axi	19	SD	Tern	13	SD	Axi	12	PR

IFN interferon, SD stable disease, IL interleukin, Suni sunitinib, /Ax/axitinib, Tern temsirolimus, PR partial response, Sora sorafenib

^aAll molecular-targeted agents were generally administered according to the standard dosing schedule, while cytokine therapy was conducted according to the schedule as previously reported [14].

^bResponse to sequential therapy was generally evaluated by computed tomography before and every 6–12 weeks after the introduction of each agent

Fig. 1 Metastatic lesions (upper arrows) in case 1 before (a–c) and 6 months after (d–f) the introduction of rechallenge with axitinib. During treatment with axitinib rechallenge, metastatic lesions were detected only in the lung and liver in case 1

Fig. 2 Metastatic lesions (upper arrows) in case 2 before (a, b) and 6 months after (c, d) the introduction of rechallenge with axitinib. During treatment with axitinib rechallenge, metastatic lesions were detected only in the lung in case 2

5]. Based on accumulated clinical data, resistance of mRCC to targeted agents is suggested to be transient, since changing targeted agents in different lines of treatment can induce disease regression, like the concept of the “resistance reset phenomenon” proposed by Hutson et al. [15]. Furthermore, the potential impact of the tumor microenvironment on reacquired sensitivity to TKIs was demonstrated in the previous preclinical studies using tumor models showing resistance to the respective agents [16, 17]. Collectively, these findings suggest that rechallenge with a specific targeted agent

could be a good option for mRCC patients during long-term sequential treatment.

In recent years, several studies have shown the potential therapeutic benefit of rechallenge with TKIs in mRCC following treatment failure with the same agents [9–12]. For example, Zama et al. treated 23 mRCC patients with sunitinib rechallenge, and reported that the objective response rate was 22% and the median progression-free survival (PFS) was 7.2 months in these patients [10]. At our institution, only two patients with mRCC described in this report received

axitinib rechallenge; however, these two showed significant responses to rechallenge with axitinib following being refractory to prior treatment with this agent. Since axitinib is currently regarded as the standard second-line agent for the treatment of mRCC patients [1, 4], axitinib rechallenge, if introduced, would be provided as $\geq$ fourth-line. Considering the multiple useful agents available for mRCC,¹ there may be a markedly increasing number of mRCC patients who will be treated with targeted agents up to $\geq$ fourth line, suggesting that the emergence of more candidates who are likely to benefit from axitinib rechallenge is expected. Furthermore, considering desirable clinical features of axitinib, including powerful antitumor activity, mild AE profile, and favorable quality-of-life status [4, 18], rechallenge with axitinib is strongly recommended for selected mRCC patients, particularly those who are scheduled to receive further agent at late line, like these 2 cases, even if other options, such as unused TKIs and sunitinib rechallenge, would be available.

It is of interest to address the mechanism underlying tumor susceptibility to TKI after prior use of the same agent. Theoretically, it could be explained by several biological phenomena, including reversion to a greater VEGF reliance with time off from TKI therapy, overcoming resistance to TKI due to inadequate target inhibition by enhanced receptor signaling and release from the selective pressure induced by TKI that possibly leads to the development of clones acquiring resistant phenotype to specific type of TKI [10]. In the two cases presented in this report, however, rechallenge with axitinib showed more pronounced antitumor activity than prior treatment with axitinib. Taken together, it is suggested that the administration of an agent with a mechanism of action different from TKI, like temsirolimus, between axitinib therapies results in a significant modulation of the activity of signaling pathways, which might provide a suitable environment for axitinib to exert its cytotoxic activity against mRCC. In fact, we previously reported different activation statuses of signal transduction pathways among RCC cells resistant to TKIs or temsirolimus [19–21].

In conclusion, to our knowledge, this is the first report describing the clinical course of mRCC patients undergoing axitinib rechallenge. In the two cases presented in this report, rechallenge with axitinib exhibited significant efficacy after being refractory to prior treatment with axitinib. Accordingly, albeit the experience involving only two cases, these findings suggest that axitinib rechallenge could be a promising therapeutic option during long-term sequential therapy against mRCC.

Compliance with ethical standards

Conflict of interest H. Miyake and M. Fujisawa have received lecture fees from Pfizer (Tokyo, Japan). K-I. Harada has declared no conflict of interest.

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