Prolonging survival in metastatic renal cell carcinoma patients treated with targeted anticancer agents: a single-center experience of treatment strategy modifications

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Introduction: *We investigated therapeutic outcomes in consecutive patients with metastatic renal cell carcinoma treated with targeted anticancer agents from 2008 to 2014 in order to determine the efficacy of adverse event management for such agents and the best sequence in which to use them.*

Materials and methods: *We analyzed 132 consecutive patients who had taken targeted anticancer agents for metastatic renal cell carcinoma. Of these, 101 patients received therapy between 2008 and 2011 (pioneer group) and 31 patients received therapy between 2011 and 2014 (contemporary group). Patients of the contemporary group were provided with aggressive adverse event management and education on such management, were treated according to a standard therapeutic strategy, and were able to receive axitinib as a second-line drug. We analyzed the incidence of hand-foot syndrome. Furthermore, we compared relative dose intensity between patients in the pioneer and contemporary groups who took sunitinib as first-line therapy. We also compared overall survival between the two groups to determine whether adverse event management improved prognosis.*

Results: *The incidence of hand-foot syndrome was significantly reduced by aggressive adverse event management. Relative dose intensity was significantly higher in the contemporary group than in the pioneer group. Median survival time was significantly longer in the contemporary group than in the pioneer group.*

Conclusion: *Our results suggest that aggressive management of adverse events associated with targeted drugs, the use of sunitinib as a first-line therapy, and the availability of axitinib as a second-line therapy all contribute to prolonged survival for metastatic renal cell carcinoma patients.*

Key Words: metastatic renal cell carcinoma, sunitinib, axitinib, adverse event

Introduction

In 2014, six targeted anticancer agents were approved for metastatic renal cell carcinoma (mRCC) treatment in Japan. However, it is often difficult to decide when to use these drugs. Although large-scale clinical trials have found sunitinib effective as a first-line therapy for mRCC,[1,2] proper sequencing for the other drugs has yet to be established.

Although targeted anticancer drugs are effective, discontinuation or dosage reduction is often necessary as a result of adverse events (AEs).[1] In order to obtain maximum benefit from these drugs, management of AEs is important.

In this study, we investigated the therapeutic outcome of consecutive mRCC patients treated with targeted drugs from 2008 to 2014; note that in 2011, we began efforts to reduce treatment discontinuation

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associated with AEs. At approximately the same time, a new targeted agent, axitinib, became available, making it easier to plan a therapeutic strategy for mRCC treatment.[3]

This article reports the efficacy of AE management in mRCC patients being treated with targeted anticancer drugs, focusing in particular on the effectiveness of sunitinib as a first-line therapy and axitinib as a second-line therapy.

Materials and methods

We retrospectively analyzed 132 consecutively treated patients who had taken targeted agents for mRCC for 3 months or longer. Patients were divided into two groups: those who were first treated between April 2008 and March 2011 (pioneer group) and those who were treated between April 2011 and April 2014 (contemporary group). The pioneer group consisted of 101 patients who were not provided with aggressive AE management or education about such management. They were treated with targeted agents selected according to the judgment of the attending physician, and were administered axitinib only as a third-line or later. The contemporary group consisted of 31 patients who were provided with aggressive AE management and education about such management. They were treated according to a standard therapeutic strategy using sunitinib as a first-line drug and axitinib as a second-line.

Regarding administration of first-line drugs, sunitinib 50 mg was administered orally (PO) every day over 4 weeks, followed by a 2 week washout period. Dose reductions, where needed, were made in steps of 12.5 mg. Sorafenib was administered continuously at a full dose of 400 mg PO twice a day, with an allowed dose reduction of 200 mg.[1,4]

Response assessment was performed by using computed tomography (CT) or magnetic resonance imaging (MRI) scans every 10-12 weeks according to the standard Response Evaluation Criteria in Solid Tumors (v. 1.0).[5] Toxicity was graded according to the Common Toxicity Criteria for Adverse Events (v. 4.0).

Adverse event management

In 2011, we began efforts to reduce treatment discontinuation associated with AEs. A treatment diary was used for AE management. The patients were asked to self-record blood pressure; the presence or absence of hand-foot syndrome (HFS), diarrhea, and general fatigue; and a number of other items, Figure 1a. Attending physicians tried to diagnose AEs at an early stage. When an AE occurred, treatments were given for each individual symptom as soon as possible. We paid special attention to HFS. A brief hospital visit was conducted for the patients before they began treatment, during which the patients were educated on how to prevent HFS by nurses and pharmacists. Patients were also provided with an original video providing lifestyle guidance, which could be viewed at any time. We also created a brochure for patients, Figure 1b. In cases of HFS, an appropriate medicine was prescribed in consultation with a dermatologist, Figure 1c.

Day								
Consultation day								
Dose (capsule size)								
Blood pressure	**morning**	/	/	/	/	/	/	/
	night	/	/	/	/	/	/	/
Blood temperature								
Fatigue								
Stomatitis								
Appetite loss								
Nausea, abdominal pain								
Bleeding from nose or mouth								
Palpitation, dyspnea								
Skin condition	**erythema**							
	pain							
	numbness							
	rhagades							
	blister							
	yellowing of the skin							
	other							
Defecation (diarrhea)								
Other								
Free space								

Figure 1a. Treatment diary.

We analyzed the incidence of HFS, which occurred in 97 patients in the pioneer group (among whom first-line therapy was sorafenib in 66 and sunitinib in 31) and 27 patients in the contemporary group (all of whom received sunitinib as their first-line therapy).

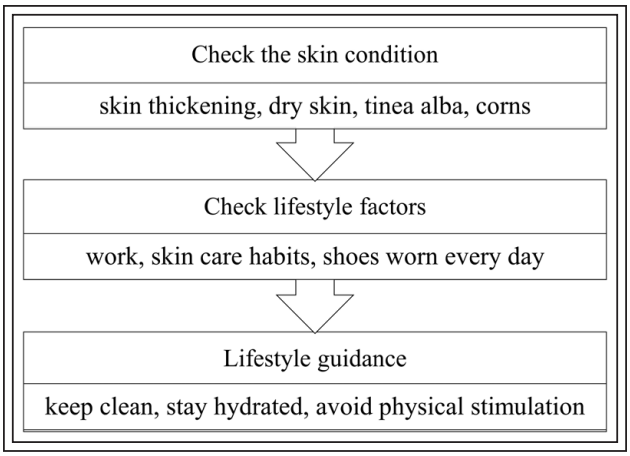

Figure 1b. Guidelines for patients.

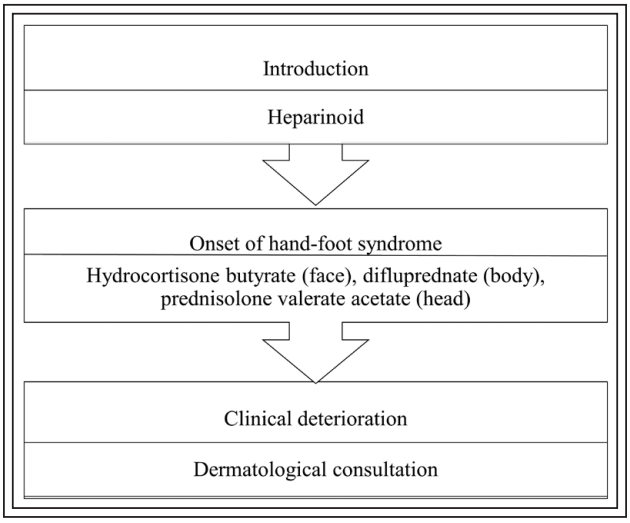

Figure 1c. Practical treatment protocol.

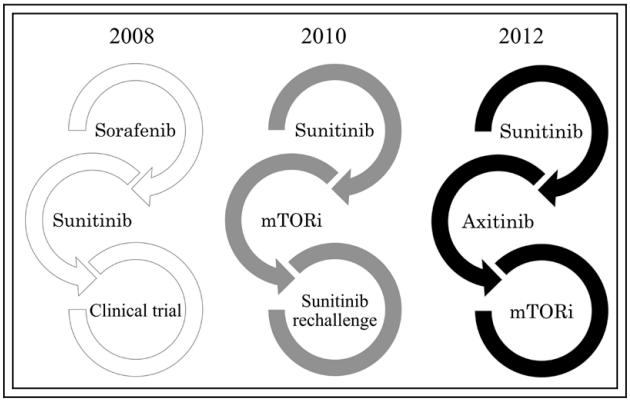

Figure 2. Treatment transition in our institute.

Therapeutic strategy

Figure 2 shows the changes in therapeutic strategy at our institute. At first, we used sorafenib as the first-line therapy and sunitinib as the second-line therapy. From 2010 onward, we usually used sunitinib as the first-line therapy, and from 2012 onward, we usually used axitinib as the second-line therapy.

Relative dose intensity

We used relative dose intensity (RDI), calculated as the percentage of the originally intended cumulative dose actually received over the treatment period, as an indicator of the effectiveness of AE management. This was done only for patients who used sunitinib for 3 months or longer, with 4 weeks on and 2 weeks off being considered the treatment period. Patients treated with sorafenib were excluded from this analysis, as none of them were members of the contemporary group.

Overall survival

We compared the overall survival of both groups. We also evaluated the effects of RDI on the survival rate of patients in both groups treated with sunitinib as first-line therapy. In addition, we examined outcomes of axitinib treatment, as axitinib became available at the same time AE management began in our institute.

Statistics

Associations of age, sex, Memorial Sloan-Kettering Cancer Center (MSKCC) criteria,[6] and observation period with HFS incidence rate were explored using the chi-square test. Differences in RDI were determined using the unpaired t-test. Overall survival (OS) was estimated using the Kaplan-Meier method, and differences were determined using the log-rank test. A p value < 0.05 was considered statistically significant. All statistical calculations were performed using Microsoft Excel.

Results

Patient background

A total of 132 patients treated with targeted anticancer drugs were included in the study. Of these, the 102 treated between January 2008 and March 2011 did not receive education on how to manage AEs associated with these drugs, whereas the 31 treated between April 2011 and April 2014 did.

Table 1 shows the characteristics of the study population according to groups. There were no statistical differences between the pioneer and contemporary groups in terms of age, observation period, or MSKCC

TABLE 1. **Patient characteristics**

	Pioneer group Jun. 2008-Mar. 2011	**Contemporary group Apr. 2011-Mar. 2014**	**p value**
Cases	102	31	
Age	64 (35-83)	65 (45-79)	
Sex			0.041
Male	92	24	
Female	10	7	
Observation period	15 (1-70)	19 (4-39)	0.321
MSKCC risk classification			0.057
Favorable	23	4	
Moderate	54	22	
Poor	22	2	
Unknown	3	3	
Drugs			
Sorafenib	72	0	
Sunitinib	52	28	
mTORi	49	19	
Axitinib	10	19	
Pazopanib	0	1	
First-line therapy			
Sorafenib	66	6	
Sunitinib	31	27	
mTORi	5	3	
Axitinib	0	1	
Second-line therapy			
Sorafenib	2	0	
Sunitinib	18	1	
mTORi	27	9	
Axitinib	2	15	

MSKCC = Memorial Sloan-Kettering Cancer Center; mTORi = mammalian target of rapamycin inhibitor

assessment. Although patients in the pioneer group were more likely to have an MSKCC risk classification of "poor," there was no significant difference overall.

Incidence of HFS

The incidence of HFS was significantly reduced in the contemporary group, Table 2. However, there was a difference in first-line therapy (sorafenib versus sunitinib) between the pioneer and contemporary groups. In general, the incidence of HFS is higher in patients using sorafenib than those using sunitinib,[1,4] therefore, we examined the patients who were treated with sunitinib as first-line therapy. The results showed no significant difference in the incidence of HFS, although it was slightly lower in the contemporary group (p = 0.067), Table 2.

RDI of sunitinib

Figure 3 shows the RDI of sunitinib in both groups. The RDI in the contemporary group was significantly higher than that in the pioneer group (68.2% versus 57.6%, p = 0.044).

Survival rate

The median overall survival was 36 months. Figure 4 shows the Kaplan-Meier estimates of survival for the pioneer and contemporary groups. The median survival time of the contemporary group (median survival undefined) was significantly longer than that of the pioneer group (30 months) (p = 0.031, log-rank test). Further, we compared the survival rates between patients who had taken sunitinib as first-line therapy, Figure 5, finding that survival time was

TABLE 2. **Incidence of hand-foot syndrome (HPS)**

	Pioneer group	Contemporary group	p value
HFS grade			
None	43 (42.6%)	26 (83.9%)	
I	17 (16.8%)	2 (6.5%)	
II	22 (21.8%)	3 (9.7%)	
III	19 (18.8%)	0 (0%)	0.0001
Sunitinib HFS grade			
None	21 (63.6%)	26 (83.9%)	
I	4 (12%)	2 (6.5%)	
II	4 (12%)	3 (9.7%)	
III	4 (12%)	0 (%)	0.067

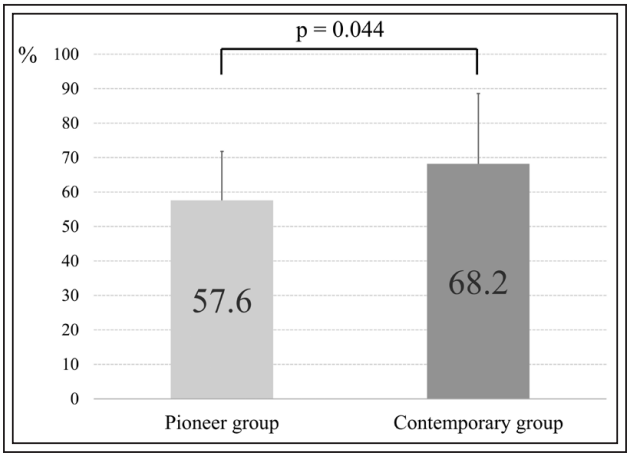

Figure 3. Sunitinib relative dose intensity.

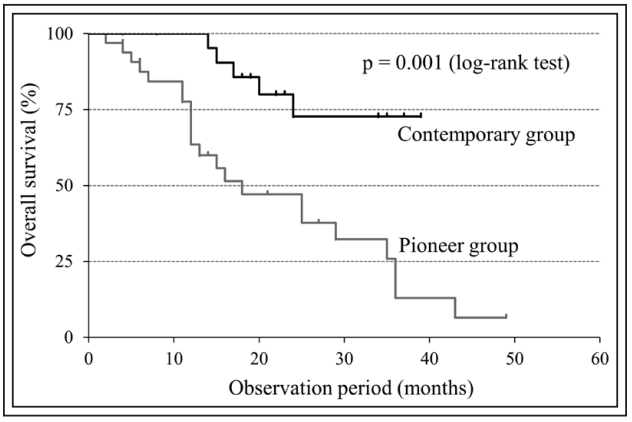

Figure 5. Overall survival in patients receiving sunitinib as first-line therapy (pioneer group versus contemporary group).

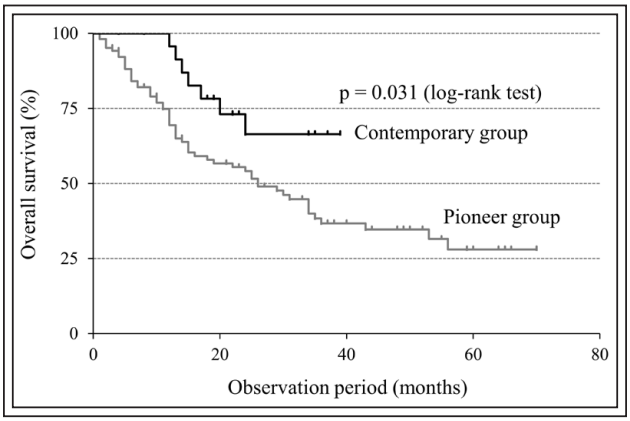

Figure 4. Overall survival (pioneer group versus contemporary group).

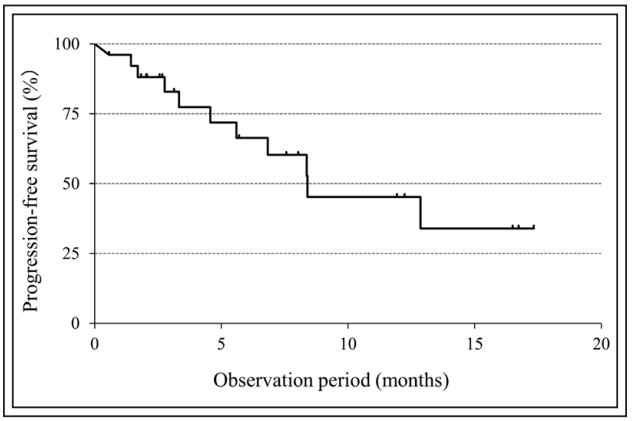

Figure 6. Progression-free survival in patients receiving axitinib treatment.

likewise significantly longer for the contemporary group (median undefined) than the pioneer group (30 months) ($p = 0.001$).

Figure 6 shows the results of axitinib treatment. Twenty-nine consecutive patients with mRCC were treated with axitinib between September 2012 and March 2014, with 17 receiving it as second-line therapy and 12 as third-line or later. Ten of the patients who received it were in the pioneer group and 19 in the contemporary group. Progression-free survival was 8.4 months (the median observation period was 10.1 months), which was a better result than in previous reports.[3-7]

Discussion

Many randomized trials[1,4] have demonstrated that targeted anticancer agents are effective for mRCC. Recent clinical studies have recommended sunitinib as the first line of therap,[1,8] and axitinib as the second line.[3] However, it is not clear whether this sequence is the best. Nevertheless, despite the deficiency of information, these drugs must be used as carefully as possible to prolong patient survival as long as possible. Accordingly, our institution began to focus on the management of AEs associated with these drugs. This management appears to have led to improved outcomes, particularly with regard to sunitinib RDI and overall survival.

Casttellano et al demonstrated that in order to obtain the maximum clinical benefit from targeted agents, effective therapy management is essential and includes optimization of dosing and treatment duration, as well as adequate side-effect management.[9] However, the many AEs associated with targeted agents often make mRCC treatment difficult. High blood pressure and hypothyroidism are relatively easy for the oncologist to diagnose and manage, so they rarely force discontinuation of therapy. On the other hand, management of HFS, diarrhea, general fatigue, and stomatitis is very difficult, and these AEs frequently lead to discontinuation. At our institute, we attempt to detect AEs early by checking the patient's treatment diary. Of all these AEs, HFS has the greatest effect on the patient's quality of life; therefore, we use aggressive management to avoid and treat it. As a result, the prevalence of HFS in our patients has been significantly reduced. However, the incidence of HFS is generally different between sunitinib and sorafenib users.[1,4] For this reason, we could not simply compare the incidence of HFS between our two study groups. Therefore, we included only patients who used sunitinib as first-line therapy in our analysis, finding that the incidence of HFS was lower in the contemporary group. Furthermore, we found that managing HFS can lead to increased sunitinib RDI. In fact, the treatment diary helped us adjust dosage or dosage interval as needed.

In this study, overall survival was 36 months, the same in a previous study of patients treated with sunitinib as first-line therapy.[10] As might be expected, our management efforts appeared to significantly prolong survival in the contemporary group; further, the same result was obtained when only patients receiving sunitinib as first-line therapy were compared between groups. However, our sample included many patients who were treated before we developed our current protocols for mRCC therapy with targeted agents; for instance, many patients were treated with sorafenib as first-line therapy, which may be inadequate,[4] and management of AEs was probably likewise often inadequate. Accumulating evidence suggests that sunitinib is the most effective first-line therapy for mRCC,[1,8] and this may also have affected our results.

Axitinib has been available in Japan since 2012,[11] when mRCC treatment options began to diversify, and large-scale clinical study have recommended it as a second-line drug.[3] Further, it is discussed that the management of AEs during axitinib therapy is also important.[12,13] We found progression-free survival with axitinib to be 8.4 months (the median observation period was 10.1 months). In this study, almost all patients treated since April 2011 received axitinib as second-line, while patients treated prior to April 2011 received it only as third-line or later. Thus, there may be a little possibility that the use of axitinib was responsible for the extended survival.

This study is a retrospective study and thus has certain limitations. Observation periods were different between groups, and the targeted agents selected were also different. Thus, no definitive conclusion can be drawn on the basis of a direct comparison of survival rates. Furthermore, patients with the MSKCC risk classification of "poor" were more numerous in the pioneer group than in the contemporary group. It is possible that this affected the difference in survival rate. In order to solve these problems, further investigation is needed.

Conclusion

In conclusion, our results suggest that aggressive management of AEs associated with targeted anticancer agents can prolong survival in patients with mRCC, and the use of a standard therapeutic strategy involving

sunitinib as the first-line and axitinib as the second-line may have been as important as AE management in our patients. However, given the limitations of our retrospective study design and dissimilar patient groups, further investigation is needed to determine the scope of these effects. □

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