Updated recommendation on molecular-targeted therapy for metastatic renal cell cancer

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Abstract. Molecular-targeted therapy was recommended for the systemic therapy of renal cell cancer (RCC) in the RCC guidelines, but these guidelines do not address the order of administration of the multiple presently available agents. There are several aspects that remain unknown regarding the optimal administration order and combination of molecular-targeted drugs. Until the optimal treatment sequence is determined by clinical trials, treatment individualization is required for each patient based on patient and disease characteristics. We herein investigate 12 cases of RCC patients who received axitinib. Axitinib was used as the first-line drug in 4 cases, second-line in 5 cases, third-line in 1 case and as a fourth-line drug in 2 cases. Partial response (PR) was observed in 4 cases (30%) and stable disease in 4 cases (30%) during axitinib treatment, with an overall response rate of 60%. The duration of PR ranged from 6 to 19 months. Based on our cases, axitinib exhibited reasonable therapeutic efficacy as first- as well as second-line treatment. However, more cases are required to draw firm conclusions.

Introduction

Molecular-targeted therapy was recommended for the systemic therapy of renal cell cancer (RCC) in the 2011 Japanese Urological Association RCC guidelines (1,2); however, these guidelines do not address the order of administration of presently available multiple agents. The European Association of Urology guidelines recommend either sunitinib or everolimus as first-line therapy, and sorafenib or everolimus as second-line therapy, although there are several aspects that remain unknown regarding the optimal administration order and combination of the multiple molecular-targeted drugs (3). At the 2015 ASCO annual meeting, the results of a comparison test of sunitinib→everolimus vs. everolimus→sunitinib were reported, indicating that the median survival rates were 29.5 and 22.2 months, respectively, concluding that sunitinib→everolimus was more effective (4,5).

Until clinical trials determine the optimal treatment sequence, treatment individualization is required for each patient based on patient and disease characteristics. In this study, we investigated 12 cases of renal cancer in which axitinib had been administered.

Patients and methods

Case series. A total of 12 patients who were diagnosed with RCC between 2005 and 2011 were reviewed (Table I). Approval was obtained from the Ethics Committee of our institution at the commencement of the study. The patients included 9 men and 3 women, with a mean age of 66 years (range, 58-79 years). Axitinib was used as a first-line drug in 4 cases, second-line in 5 cases, third-line in 1 case and as a fourth-line drug in 2 cases. Partial response (PR) was observed in 4 cases (30%) and stable disease in 4 cases (30%) during axitinib treatment, with an overall response rate of 60%. The duration of PR ranged from 6 to 19 months.

Of the 4 PR cases, the case 1 patient had received axitinib as first-line therapy, and he had not received any other molecular-targeted drugs; in 2 PR cases, axitinib was administered as second-line treatment; in the remaining PR case, axitinib had been followed by panitumab, with which a clinical response was achieved.

Case reports. Case 6 was a 61-year-old male patient. At the initial visit, an 8-cm mass was identified, extending from

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Table I. Summary of the investigated 12 cases.

Case no.	Age, years	Sex	Drugs (sequence)	Metastastic sites	Effectiveness	PR duration, months
1.	79	Male	A	Lung, adrenal	PR	6
2.	59	Male	Su→A→E	Lung, bone	PD	
3.	73	Male	Su→A	Lung, liver	PR	9
4.	69	Male	Su→A	Kidney, lung, pancreas	PR	6
5.	47	Male	INF→Su→A	Lung, lymph nodes	SD	
6.	61	Male	A→P	Bone, pleural cavity	PR	19
7.	58	Female	Su→A	Lung, lymph nodes, brain, bone	PD	
8.	76	Female	Su→A	Liver	SD	
9.	76	Female	INF→So→UFT→A	Lung, lymph nodes	SD	
10.	64	Male	A→E→INF→Su →So	Adrenal, pancreas	PD	
11.	67	Male	GC→GDC→E→A	Lung, liver, bone	SD→PD	8 (SD, collecting ductal carcinoma)
12.	63	Male	A	Bone, lung	PD	

A, axitinib; Su, sunitinib; E, everolimus, INF, interferon; So, sorafenib; P, pazopanib; GC, gemcitabine and carboplatin; GDC, gemcitabine, docetaxel and carboplatin; PR, partial response; PD, progressive disease; SD, stable disease.

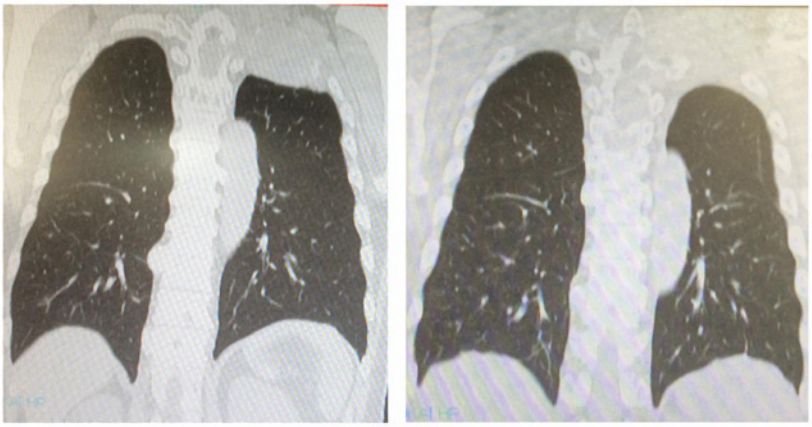

Figure 1. Case 6: Computed tomography revealed a 3-cm tumor in the inferior pole of the right kidney (left panel, pretreatment; right panel, post-treatment).

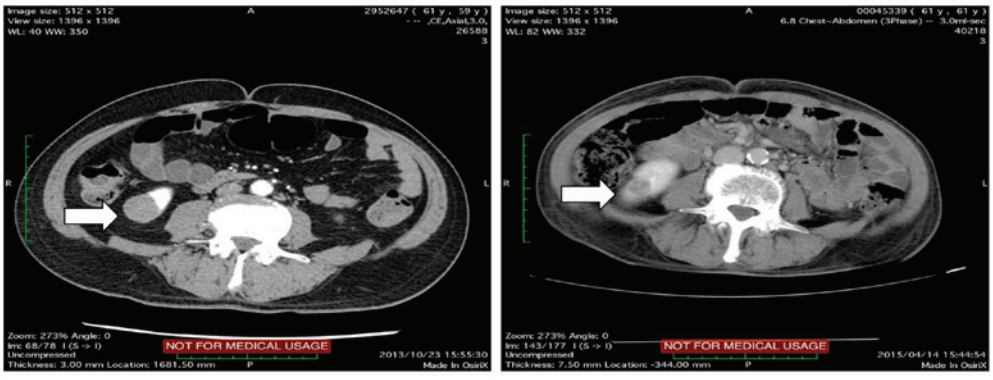

Figure 2. Case 6: Computed tomography revealed that, although the renal lesion was reduced, the bone metastatic lesion exhibited progression (left panel, pretreatment; right panel, post-treatment).

the posterior aspect of the upper left lung to the chest wall, infiltrating the ribs and the Th1 vertebral body, with partial compression of the spinal cord. The computed tomography (CT) scan revealed a 3-cm tumor in the inferior pole of the

right kidney (Fig. 1). CT-guided tumor biopsy of the lung mass revealed RCC metastasis. Axitinib was administered at 10 mg/day; after 10 days, the dose was increased to 12 mg/day, and to 14 mg/day 2 weeks later. At the time of admission to the hospital the patient was bedridden. Following intensive rehabilitation, the patient was able to use a wheelchair and even to leave his house. The treatment was continued on an outpatient basis. However, due to progression of metastatic bone disease (Fig. 2), the patient was readmitted to the hospital. He currently remains alive and is on pazopanib treatment.

We encountered one case of collecting duct carcinoma, which is a type of RCC refractory to cytotoxic and molecular-targeted therapy. However, case 11, a 67-year-old male patient, achieved PR. The patient visited our hospital complaining of hematuria. Based on the results of the pathology, he was diagnosed with renal collecting duct carcinoma with renal hilar lymph node metastasis. After 4 months, the patient underwent left nephrectomy and the subsequent pathological diagnosis was pT3, ly1, v1, INFβ, pN2. Four weeks after the operation, the patient was started on adjuvant GC chemotherapy (gemcitabine 1,200 mg and cisplatin 300 mg) (6) and completed four cycles. Six months postoperatively, multiple pulmonary metastases were identified on CT, and metastasis to the right pelvic bone was identified by bone scintigraphy. GDC chemotherapy (gemcitabine 1,200 mg, docetaxel 80 mg and cisplatin 300 mg) was initiated 4 weeks later (7). The results of the CT conducted on June 20, 2012 confirmed peritoneal dissemination, progression of multiple lung metastases and revealed metastatic liver disease. Two months later the patient was administered 10 mg everolimus. After administration of everolimus for 3 months, the blood sugar level was found to be high, which was considered to be an adverse event (AE) and the drug was discontinued, followed by normalization of the patient's blood sugar levels, after which time everolimus was resumed at a reduced dose of 5 mg. At the 8-month follow-up the patient remained progression-free, which is unusually long for renal collecting duct cancer.

Discussion

Based on our cases, axitinib demonstrated reasonable therapeutic efficacy as first- as well as second-line treatment. However, to draw a firm conclusion, more cases must be accumulated.

Procopio *et al* reviewed 13 cases of renal collecting duct carcinoma. Renal collecting duct carcinoma patients (median age, 57 years) comprise 3.4% of all metastatic RCC (mRCC) patients, with a median survival time of 4 months, with only 3 cases having survived 6-33 months (8-11). The disease-specific survival of our patient (case 11) was 13 months from the time of the appearance of metastases. In a study on the administration of sunitinib, axitinib, sorafenib, interferon and temsirolimus as first-line drugs in 4,736 mRCC cases, a reduction ratio of >7-8% of the tumor was associated with a relatively good prognosis (12). Moreover, in a study on the combined use of tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin inhibitors in 153 cases of metastatic clear cell RCC (ccRCC), comparing the combined use of lenvatinib and everolimus with the use of lenvatinib alone and with the use of everolimus alone, achieved a survival of 13.1, 7.5 and 8.5 months, respectively, indicating that combination therapy was superior to single-agent treatment (13). Furthermore, in a study of 108 cases of non-ccRCC, survival with sunitinib was 8.3 months and that with everolimus 5.6 months, indicating that sunitinib was superior; however, for poor-risk RCC, survival was 4.0 and 6.1 months for sunitinib and everolimus, respectively, indicating that everolimus was better for poor-risk cases (14).

A study of the programmed cell death protein-1 (PD-1) antibodies for RCC was also conducted (15-17). The therapeutic effects of pazopanib and sunitinib in RCC cases expressing PD-1 were significantly inferior to the PD-1 low-expressing cases, and the median survival time was also shorter (18). Nivolumab (PD-1-inhibiting antibodies) was investigated in 91 cases, and it was effective in programmed death-ligand-1 (PD-L1)-positive as well as -negative cases (based on immunostaining of cancer cells). While a 71% 1-year survival was attained by both positive and negative cases, the 2-year survival rates were 64 and 48%, respectively (19). In addition, the mPFS of the cases in whom anti-PD-1 treatment had not been effective and in whom TKIs had been administered was 6.9 months, indicating that it may be safely administered (20). Immunostaining for PD-L1 was positive in 51% of spindle cell cancer cases, whereas 100% of the cases that contained a ccRCC component were positive (18). However, due to the fact that only 17% of the ccRCCs that did not contain a spindle cell carcinoma component were PD-L1 positive, there is a possibility that PD-1 antibodies are effective in spindle cell cancer, which has poor prognosis (21). A study to predict therapeutic effect based on immunostaining for PD-L1 of tumor cells has been conducted. However, cases were successfully treated irrespective of positive or negative immunostaining; thus, no conclusion was reached at that time (22). Moreover, it is considered that the more gene mutations the cancer cells harbour, the more successful the immunotherapy. Further research on immune therapy that includes PD-L1 antibodies is expected in the near future.

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