Review Article

Current status of pharmacotherapy against metastatic renal cell carcinoma in Japan

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Abstract: So far, metastatic renal cell carcinoma has been one of the most treatment-resistant cancers. The extensive use of cytokines, such as interferon-α and interleukin-2, were carried out for metastatic renal cell carcinoma. However, significant advances in understanding the molecular mechanisms underlying renal cell carcinoma have led to the development of molecular target-based drugs, which were desperately awaited for a long time, and now two types of molecular target-based drugs are available. Two vascular endothelial growth factor receptor tyrosine kinase inhibitors and two mammalian target of rapamycin inhibitors have been approved and available in Japan. The molecular target-based drugs have unique and characteristic adverse events, whose profile are not well understood in Japanese patients, because most of the clinical trials were carried out in Europe and America. In contrast, immunotherapy is being reconsidered in the selection of more appropriate patients or as a combined treatment form with other drugs, because of few complete responses obtained and unexpected adverse events by molecular targeted treatments. We have several molecular targeted-drugs available at present and will have more, and we will actually use these drugs in various clinical settings, such as the presurgical setting, the adjuvant setting, sequential administration and combined administration, in addition to cytokines. Therefore, we need more elaborate studies to obtain the optimal treatment methods to maximize the effect of such agents to extend overall survival while maintaining quality of life of metastatic renal cell carcinoma patients. In this article, we reviewed the issues related to the current status of pharmacotherapy available for metastatic renal cell carcinoma.

Key words: angiogenesis inhibitors, immunotherapy, mammalian target of rapamycin inhibitors, renal cell carcinoma, targeted therapy.

Introduction

In Japan, pharmacotherapy for advanced RCC began in the 1960s in the form of progesterone administration; although since 1987, this was replaced by the extensive usage of cytokines, such as IFN-α, and since 1999 by IL-2. These options, however, only exerted limited effects, therefore more useful agents from the point of view of tolerance and convenience were anticipated. In particular, the development of new treatment methods with different mechanisms of action were desperately awaited by patients who were either unfit for or unresponsive to immunotherapy, who therefore had no further treatment options. To shed light on such situations, target-based drugs medicine has emerged and has now become available as a new therapeutic tool (Fig. 1). Many molecular target-based drugs have been approved one after another since 2006 in the USA, and since 2008 in Japan. Currently, two VEGFR TKI and two mTOR inhibitors have been approved and are available in Japan. Furthermore, clinical trials of other new drugs are also ongoing, and these drugs are expected to become available in the near future.

We searched the PubMed database for publications using “metastatic renal cell carcinoma” and “targeted therapy,” “metastatic renal cell carcinoma” and “cytokine therapy,” “metastatic renal cell carcinoma” and “risk factors,” or “non-clear renal cell carcinoma” and “chemotherapy” as keywords. Cross-references were used for search completion. We
screened all studies on the titles and abstracts, we selected those that related to the present article, and then we also included abstracts from the proceedings of the annual meeting of AUA or ASCO. In the present review, issues related to pharmacotherapy available for treating MRCC are outlined and discussed.

**Stratification**

Despite prognostic factors being originally designed to predict patient outcomes, such as progression, recurrence or death either in the presence or absence of treatment, it is well recognized that these factors are also useful for classifying risks of patients who participate in clinical trials for new drug evaluations. Motzer’s group in the MSKCC was the first to describe the following five risk factors for advanced RCC: (i) decrease in the Karnofsky Performance Status (\(< 80\%\)); (ii) low serum hemoglobin concentration (male/11.3 g/dL and female/11.5 g/dL); (iii) high serum corrected calcium level (\(> 10\) mg/dL); (iv) high serum LDH level (\(> 1.5\) times upper limit of normal); and (v) without nephrectomy. They classified patients with zero risk factors into low-, those with one or two risk factors into intermediate- and those with three or more risk factors into high-risk groups. Later on, “without nephrectomy” was replaced by “time from initial diagnosis to IFN-\(\alpha\) treatment of less than 1 year” in the new Motzer’s criteria. According to this risk classification, OS over 2 years was reported to be 75\% in the low-risk group, 53\% in the intermediate-risk group and 7\% in the high-risk group.

In addition, several other prognostic factors and risk classifications have been proposed (Table 1). CRP, a marker of inflammation, was reported to negatively correlate with anemia, and therefore did not appear to be an independent prognostic factor. Similarly, thrombocytosis and neutrophilia did not seem to be independent, as they are related to inflammation very generally. However, these new classifications are very similar to the MSKCC risk classification, with only small modifications being made. Therefore, the MSKCC risk classification still continues to be the standard criteria, even in the age of molecular target treatment for MRCC today.

**MRCC in Japan**

Naito et al. retrospectively studied prognoses of 1463 Japanese MRCC patients and prognostic factors when cytokines were used for treatment. They classified patients into three risk groups according to Motzer’s five prognostic factors and compared their prognoses with Motzer’s study. Although following prospective verifications were required, they reported their risk classification, which included CRP, to be useful especially among Japanese MRCC patients. According to their study, the median OS of total patients (21.5 months) was approximately twice as long compared with that observed in Motzer’s study. The median OS of

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**Fig. 1** Developments in pharmacotherapy for RCC. Events in foreign countries are shown in blue, events in Japan are shown in red.
each group was also approximately twice as long compared with corresponding groups in Motzer’s study: 55.3 months versus 30 months, 29.6 months versus 14 months, and 9.8 months versus 5 months in the low-, intermediate- and high-risk groups, respectively. Such differences might be explained by the following reasons: ethnic difference: in Motzer’s study, most patients were Caucasian or African-Americans. Difference in treatment strategy: first, nephrectomy was carried out on more patients in the Naito et al. study compared with Motzer et al. (80.5% vs 55%). Second, almost all patients were given cytokine-based therapy, which was continued even after disease progression. Third, more patients seemed to have received metastasectomy in the Naito et al. study (20.8%). Lead time bias: the number of metastatic nests-organs and the ratio of multiple/single metastasis (29.6% vs 61%) were less in Naito’s study compared with Motzer’s study, which suggests that earlier discovery and treatment for the metastatic disease was possible by Naito et al. The most important reason is thought to be lead-time bias. It is noteworthy that obvious differences in health insurance schemes might have contributed to the second and third reasons.

Some AE, including hypothyroidism, have been reported to appear after long-term administration of molecular targeted drugs (median time 50 weeks). In contrast, a group of Japanese MRCC patients whose OS exceeded 50 months was actually present. Because AE occurring during longer-term administration (more than 50 months) of those molecular target-based drugs have not yet been clarified, longer-term careful monitoring of AE is required.

**Immunotherapy**

Since the approval for use on RCC by the Ministry of Health in 1987, IFN-α, in particular the natural type, has been widely used in Japan, and IFN-α monotherapy for advanced RCC was recommended as grade A in the clinical practice guidelines for the management of RCC, compiled by JUA (2007 edition). However, the response rate and survival benefit achieved by this cytokine are only 6–15% and 3–5 months respectively, which are not satisfactory levels.

Recently, a SNP analysis carried out by Ito et al. suggested that IFN-α is still effective in a selected group of MRCC patients. The retrospective analysis for finding out SNP that correlate with good responders to IFN-α in Japanese MRCC patients showed that a SNP in STAT3 gene is most significantly associated with better response to IFN-α. If the CC genotype in rs4796793, which is located in the 5’ flanking region of STAT3, is used as a predictive marker, positive and negative predictive values would be 52.8% and 88.2% respectively. Furthermore, it is suggested that IFN-α might be effective for Japanese patients in comparison with European and American patients, as a result of a higher frequency of the CC genotype among the Japanese compared with Western populations. Therefore, IFN-α monotherapy is expected to remain as an effective therapeutic option for MRCC, given that it is administered to an appropriate group of patients.

In contrast, although ORR of IL-2 treatment is approximately 15%, which is comparable to that of IFN-α.

### Table 1  Risk factors in typical risk classifications

| Motzer (1999) | Motzer (2002) | Naito (2009) | Heng (2010) | Patil (2010) (PFS) |
|--------------|--------------|--------------|-------------|-----------------|
| Corrected    | Corrected    | Corrected    | Corrected   | Corrected       |
| Serum calcium| Serum calcium| Serum calcium| Serum calcium| Serum calcium   |
| Serum        | Serum        | Serum        | Serum       | Serum           |
| LDH          | LDH          | LDH          | Performance | Performance     |
| Performance  | Performance  | Performance  | Status      | Status          |
| Status       | Status       | Status       | Anemia      | Anemia          |
| Anemia       | Anemia       | Time from initial visit to metastases | Time from diagnosis to treatment | Time from diagnosis to treatment |
| Time from diagnosis to treatment | Serum CRP | Thrombocytosis | Neutrophilia | Presence of bone metastases |

*Time from initial visit to metastases" is located in the same line of “Time from diagnosis to treatment”, because they are similar situations in Japan.
long-term CR is attainable in up to 5% of MRCC. Hence, this cytokine was also recommended in the 2010 edition of the EAU guideline as a grade C option for use in the low-risk group whose histology is clear cell type. However, it is to be noted that unlike in Western countries, low dosage administration is the only option officially approved for IL-2 treatment in Japan. Therefore, the aforementioned evidence of prognosis might not be directly applicable to the clinical setting in Japan. For instance, it is known that high-dose IL-2 treatment induces long-term CR, but it is not yet confirmed whether this is also the case for low-dose IL-2 treatment. OS of the group with IL-2 treatment exceeded that of IFN-α treatment (34.7 months vs 24.9 months) in a subanalysis regarding the benefits of cytokine treatments in the study by Naito et al. In addition, it is known that cytokine treatment is more effective for lung metastases compared with other metastasized organs in Japanese patients.

Today, as discussed in detail later in the present review, despite molecular targeted based drugs, such as sorafenib and sunitinib, being widely available for MRCC, CR is hardly obtainable as a result of their action mechanisms. We also realized that these reagents are accompanied by a lot of unexpected AE. Thus, cytokine therapy in the first-line setting has been reconsidered as a useful option, and prospective studies evaluating predictive factors for this therapy are currently ongoing. Therefore, evidence from Japanese patients, to whom cytokine therapy seems to be relatively effective, might become more important for establishing ethnically-tailored therapeutic strategies in the future.

**Molecular target-based treatment**

Molecular targeted VEGFR TKI, such as sorafenib and sunitinib, and mTOR inhibitors, such as everolimus and temsirolimus, were approved for the treatment of RCC in Japan in 2008 and 2010, respectively. Action mechanisms of these molecular target-based drugs are schematically shown in Figure 2.

It can be said that the development of molecular targeted-based drugs for RCC originated from the discovery of VHL, the gene for VHL disease, in 1993. VHL disease is an autosomal dominant tumor syndrome, which causes the formation of hemangioma in the retina and central nerve, and formation of pheochromocytoma and cystic disease in the kidney, pancreas and epididymis. In addition to these benign tumors, CCRCC also develops in 30–50% of VHL patients. The VHL gene product, pVHL, is a component of the VCBCR complex, which contains elongins B and C, Cul2 and Rbx1. This complex functions as an E3 ubiquitin ligase and recognizes hydroxylated HIF-α in normoxia, followed by its ubiquitination and destruction. Inactivation of the VHL gene is the basis of familial inheritance of VHL disease. Patients of VHL disease inherit a mutation in one copy of VHL that would result in loss-of-function of pVHL. Over time, sporadic mutation in the second copy of the VHL gene can lead to total loss of pVHL function, which in turn causes aberrant and prolonged accumulation of HIF-α. HIF-α forms a heterodimer with HIF-β, which then activates transcription of genes, such as VEGF and Cyclin D1, that can drive tumor development. In fact, the VHL gene is also the most frequently mutated gene in sporadic CCRCC.
Biallelic inactivation of VHL including deletion, mutation and hypermethylation, is found in more than 70% of sporadic CCRCC.21 Aberrant expression of VEGF, a major HIF target gene, induces abnormal angiogenesis, which is indispensable for the development and maintenance of tumors including RCC. Therefore, targeting VEGF signaling or HIF itself in CCRCC where the VHL gene is frequently mutated is a rationalized therapeutic strategy, and VEGFR TKI, such as sorafenib and sunitinib, are theoretically considered to exert an antitumor effect mainly by attenuating angiogenesis. As a matter of fact, sorafenib was originally identified as a potent inhibitor of Raf kinase, but it was later shown to have potent inhibitory effects on RTK, including VEGFR-1/2/3, PDGFR-β, Flt-3 and c-Kit. Sunitinib targets a similar profile of kinases, including VEGFR-1/2/3, PDGFR-α/β, Flt-3, CSF-R1, c-Kit and RET. Hence, VEGFR TKI appear to function as multi-targeted drugs for CCRCC.

In addition to VEGFR TKI, two mTOR inhibitors, temsirolimus and everolimus, are also molecular targeted drugs available for the treatment of RCC. mTOR was originally discovered as a target of rapamycin, which is a macrolide antibiotic produced by ray fungi.22 It was confirmed later that this reagent shows antitumor and immunosuppressive activity by inhibiting proliferation of tumors and T cells, respectively.23–26 mTOR is a serine/threonine kinase, which is located downstream of PI3K/AKT that phosphorylates S6 kinase and 4E-BP1, thereby controlling a wide range of cellular processes. Temsirolimus and everolimus also inhibit mTOR because of their structural similarity to rapamycin. In particular, everolimus has been used as an immunosuppressive agent for heart transplantation in Japan27 because of its immunosuppressive property. As the antitumor effect of these mTOR inhibitors is known to be exerted strongly in VHL-null RCC-derived cell lines, they seem to hamper tumor growth primarily by suppressing HIF-α expression.28 It could therefore be understood that these rapalogs inhibit both angiogenesis and tumor cell proliferation through mechanisms that differ from VEGFR TKI. Regarding the mechanism for aberrant mTOR activation in RCC, it is widely recognized that PTEN, a negative regulator of the PI3K/AKT pathway, is frequently inactivated in RCC as in other cancers, and it seems to contribute to abnormal mTOR activation in RCC.29,30

Regarding the clinical use of molecular targeted drugs, their positions in MRCC treatment are listed in Table 2.12 In terms of sorafenib, a randomized phase II trial led by Escudier et al. showed that it provides a PFS outcome similar to IFN-α when used in the first-line setting (5.7 months vs 5.6 months).31 Furthermore, it offers better clinical benefit compared with placebo in patients of low and intermediate risk groups who failed cytokine therapy according to a randomized phase III clinical trial that tested sorafenib against placebo (5.5 months vs 2.8 months).32 Hence, sorafenib is recommended as the only agent in the second-line setting for patients with MRCC who have failed cytokine treatment, including IFN-α. In contrast, sunitinib is recommended as an option in the first-line setting for CCRCC with low or intermediate risk, because sunitinib outperformed IFN-α in PFS when given to CCRCC patients of such risk groups in the first-line setting (11 months vs 5 months).33 Sunitinib also significantly outperformed IFN-α in ORR (31% vs 6%), which is to our knowledge, the greatest reduction rate in tumor volume achieved by any of the four molecular targeted drugs approved in Japan.33,34 Therefore, its use in the presurgical setting can also become a subject of clinical trials. Regarding the positioning of temsirolimus, even though no difference in ORR was observed, PFS by either the drug itself or in combination with IFN-α exceeded IFN-α alone; 3.8 months versus 3.7 months versus 1.9 months assessed by the site investigators, and 5.5 months versus 4.7 months versus 3.1 months by independent radiologists. With regard to OS, temsirolimus alone showed better outcome than in combination with IFN-α or IFN-α alone (10.9 months vs 8.4 months vs 7.3 months).35 It is of note that because 69% of registered patients in this clinical trial belonged to the high-risk group, temsirolimus became recommended in the first-line setting for patients in this risk group.35 Furthermore, this study contained patients with NCRCC who made up to 20% of total patients, and showed that temsirolimus was more effective on NCRCC than on CCRCC in terms of OS in comparison with IFN-α. Temsirolimus alone outperformed IFN-α in OS in the subanalysis (11.6 months vs 4.3 months).35 As for the positioning of everolimus, it is recommended as an option in the second-line setting for patients who have received prior VEGFR TKI treatment, because there was a significant difference between everolimus and placebo in the patient group that showed resistance to prior sorafenib or sunitinib treatment (4.9 months vs 1.9 months).36

Tumor reduction rates of molecular targeted drugs in phase III RCT are shown in Table 3.32,33,35,36 VEGFR TKI were more effective than mTOR inhibitors in terms of tumor reduction rate, and amongst the TKI, sunitinib was the most effective as it achieved an approximately 30% reduction rate.32,33,35,36 It is reported that sunitinib treatment in the

| Table 2 | First- and second-line systemic therapy in MRCC from EAU guidelines 2010 |
|---|---|---|
| Treatment | Risk or prior treatment | Recommended agent |
| First-line therapy | Low or intermediate risk | Sunitinib |
| High risk | Temsirolimus |
| Second-line therapy | Prior cytokine therapy | Sorafenib |
| Prior VEGFR therapy | Everolimus |
| Prior mTOR inhibitor therapy | Clinical trials |
presurgical setting enabled 21% (4/19 patients) of inoperable advanced RCC patients to undergo nephrectomy.37 PFS of patients who received molecular targeted drugs in phase III RCT is shown in Table 4.32,33,35,36 It is noteworthy that PFS of molecular targeted drugs is generally approximately twice the length of the control. The result of the domestic examination with sorafenib was slightly better than the foreign study (14.7% vs 10% in ORR, 7.5 months vs 5.5 months in PFS),32,38 whereas the domestic study of sunitinib was almost equal to that of the foreign study (48% vs 31% in ORR, 11.5 months vs 11 months in PFS).33,39

Reported AE of the molecular targeted drugs are shown in Table 5. Relatively frequent AE of sorafenib were diarrhea, rash, HFS, fatigue and alopecia.32 Incidences of serious AE as a result of sorafenib, such as angina and cardiac ischemia/infarction (3%), have also been reported.32 In the case of sunitinib, AE appeared to be more variable and characteristic compared with sorafenib. In particular, hematological toxicities, such as anemia, leukocytopenia and thrombocytopenia, were often observed during sunitinib treatment. Other frequent AE with sunitinib included elevated levels of lipase and amylase, fatigue, diarrhea, hypertension and hypothyroidism.7,33 Reduction in cardiac output was also seen in 10% of patients including 2% of those with grade 3 AE.33 The reason why sunitinib shows such a broad and unique AE profile might presumably be because of its action mechanism that blocks a wider range of RTK compared with sorafenib. Sorafenib seems to be relatively well tolerated by aged patients, because the AE profile of sorafenib in patients above the age of 70 years was similar to that in patients below the age of 70 years.40 In contrast, sunitinib appears to be more tolerable for patients with brain metastasis or patients with unfavorable prognosis, because the AE profiles of sunitinib in those cases were comparable to that in the total patient group.41 In the case of mTOR inhibitors (temsirolimus and everolimus), frequent AE reported so far include asthenia, rash, anemia and stomatitis.36,42 Digestive symptoms, such as nausea, anorexia and diarrhea, were also observed.36,42 Infection, hyperglycemia and hypercholesterolaemia were characteristic AE for mTOR inhibitors.36,42 Their immunosuppressive property and the resulting compromised host immune system might be responsible for

### Table 3 Tumor shrinkage in phase III RCT

|          | Sorafenib | Placebo | Sunitinib | IFN | Temsirolimus | IFN | Everolimus | Placebo |
|----------|-----------|---------|-----------|-----|-------------|-----|------------|---------|
| n 451    | 452       | 375     | 375       | 209 | 207         | 272 | 138        |
| Favorable| 52%       | 50%     | 38%       | 34% | 0%          | 0%  | 29%        | 28%     |
| Intermediate| 48%       | 49%     | 56%       | 59% | 31%         | 25% | 56%        | 57%     |
| Poor     | 0%        | 0%      | 6%        | 7%  | 69%         | 75% | 15%        | 15%     |
| Not assessable | 0%     | 1%      | 0%        | 0%  | 0%          | 0%  | 0%         | 0%      |
| CR       | 1%        | 0%      | 0%        | 9%  | 5%          | 1%  | 0%         | 0%      |
| PR       | 10%       | 8%      | 31%       | 6%  | 6%          | 6%  | 9%         | 5%      |
| ORR      | 11%       | 8%      | 31%       | 6%  | 9%          | 5%  | 1%         | 0%      |

The characters of cases on comparison were described briefly as following. The comparison was carried out with sorafenib versus placebo in cytokine-refractory MRCC patients, Sunitinib versus IFN in untreated MRCC patients with favorable/intermediate prognostic features, Temsirolimus versus IFN in untreated MRCC patients with poor/intermediate prognostic features and everolimus versus placebo in MRCC patients having progressed during VEGFR TKI therapy with either sunitinib or sorafenib.

### Table 4 PFS in phase III RCT

|          | Sorafenib | Placebo | Sunitinib | IFN | Temsirolimus | IFN | Everolimus | Placebo |
|----------|-----------|---------|-----------|-----|-------------|-----|------------|---------|
| n 451    | 452       | 375     | 375       | 209 | 207         | 272 | 138        |
| Favorable| 52%       | 50%     | 38%       | 34% | 0%          | 0%  | 29%        | 28%     |
| Intermediate| 48%       | 49%     | 56%       | 59% | 31%         | 25% | 56%        | 57%     |
| Poor     | 0%        | 0%      | 6%        | 7%  | 69%         | 75% | 15%        | 15%     |
| Not assessable | 0%     | 1%      | 0%        | 0%  | 0%          | 0%  | 0%         | 0%      |
| PFS (M)  | 5.5       | 2.8     | 1         | 5.1 | 3.8         | 1.9 | 4          | 1.9     |
| Favorable| N.D.      | N.D.    | 14.5      | 7.9 | N.D.        | N.D. | N.D.       | N.D.    |
| Intermediate| N.D.    | N.D.    | 10.6      | 3.8 | 7           | 5.6 | N.D.       | N.D.    |
| Poor     | N.D.      | N.D.    | 3.7       | 1.2 | 5.1         | 2.3 | N.D.       | N.D.    |

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With regard to metabolic abnormalities, it could be explained by the fact that mTOR functions as a sensor of energy metabolism. Hence, regular laboratory tests are required to monitor onset or exacerbation of metabolic disorders, such as diabetes mellitus. Grade 3 or severe pneumonitis (3%) and infectious disease (3–5%) can lead to a fatal outcome, therefore careful observation is required.36,42 Regarding interstitial lung disease, it is necessary to check respiratory symptoms and to examine a chest computed tomography scan on a regular basis for early detection. Interestingly, considerable ethnic differences in AE profiles were also observed. Although HFS was observed in 30% of patients including grade 3 or 4 events (4%) in the TARGET study, whereas it occurred in up to 55% of patients including grade 3 or 4 (9.2%) in the domestic study for sorafenib.32,38 Hypertension was observed in 17% of patients including grade 3 or 4 events (4%) in the TARGET study, whereas it occurred in up to 32.8% of patients including grade 3 or 4 (16.8%) in the domestic study for sorafenib.32,38 Frequency of grade 3 or 4 thrombocytopenia associated with sunitinib exceeded 50% in Japanese patients, although it was 7.7% in Western countries.33,39 Stomatitis was observed in 26% of Western patients, but was observed in 52% of Japanese patients.33,39 Similarly, HFS was observed in 6% of Western patients, but was observed in 44% of Japanese patients.33,39 These differences in the frequency and severity of AE between patients in Western countries and in Japan, which is presumably due to differences in genetic background, has emerged as the result of clinical trials and postmarketing surveillance in Japan. Therefore, data obtained in Western countries cannot be directly applied to Japanese patients.

Table 5: Adverse effect of molecular targeted drugs

| Toxicity          | Drugs    | Incidence     | Management                                                                 |
|-------------------|----------|---------------|-----------------------------------------------------------------------------|
| Fatigue           | All      | 20–50% all grades | Dose interruption/reduction; eliminate other treatable causes such as anemia, hypothyroidism. |
|                   |          | 3–12% ≥ grade 3 |                                                                             |
| Hypertension      | Sunitinib| 17–26% all grades | Early and aggressive BP management with dose titration of existing meds and/or additional antihypertensive therapy. |
|                   |          | 3–12% ≥ grade 3 | All classes of antihypertension agents can be effective.                    |
|                   | Sorafenib| 17–53% all grades | Dietary modifications (bland foods). Bulking agents (Benefiber, Metamucil).   |
| Diarrhea          | Sunitinib| 1–5% ≥ grade 3 | Loperamide or diphenoxylate scheduled.                                      |
|                   | Sorafenib| 20–30% all grades | Moisturizing agents, such as Bag Balm, Udder Cream, Eucerin, Biafine.        |
| Hand-foot skin reaction | Sorafenib | 5–6% ≥ grade 3 | Grade 3 (interfering with ADL) generally requires holding medication.       |
| Mucositis         | All      | 7–40% all grades | Dietary modifications (bland foods).                                        |
|                   |          | 1–3% ≥ grade 3 | Lidocaine solution. Nystatin solution for clinical mucositis.               |
| Dyspnea           | Sorafenib| 7–72% all grades | Evaluate for nondrug-related causes.                                        |
|                   | Temsirolimus | 1–9% ≥ grade 3 | Consider underlying pneumonitis if mTOR inhibitor therapy; consider steroid treatment. |
| Neutropenia       | Sunitinib| 7–72% all grades | Dose interruption if severe. Neutropenic precautions as appropriate.        |
|                   | Temsirolimus | 0–11% ≥ grade 3 | Prophylactic growth factors not recommended.                                |
| Thrombocytopenia  | Everolimus| 6–65% all grades | Dose interruption if severe.                                                |
|                   | Sunitinib | 1–8% ≥ grade 3 |                                                                             |
|                   | Temsirolimus| 11–12% ≥ grade 3 |                                                                             |
|                   | Everolimus| 26–50% all grades | Dietary modifications.                                                      |
| Hyperglycemia     | Temsirolimus| 11–12% ≥ grade 3 | Standard medications depending on abnormality.                             |
|                   | Everolimus| 27–71% all grades | Dietary modifications.                                                      |
| Hypertryglyceridemia | Temsirolimus | 1–3% ≥ grade 3 | Standard medications depending on abnormality.                             |
|                   | Everolimus| 24–76% all grades | Dietary modifications.                                                      |
| Hypercholesterolemia | Temsirolimus | 1–3% ≥ grade 3 | Standard medications depending on abnormality.                             |

Modified from Linehan MW, Figlin RA, Pinto P. Recent advances in diagnosis and management of kidney cancer. AUA 69IC. 2010.
**Sequential or combined administration**

There is a limit to cytokine therapy, where effectiveness is known to be approximately 10–20%. Although molecular targeted drugs exert significant and excellent antitumor effects in comparison to cytokine therapy, it is difficult to attain CR by single agent administration. Therefore, when resistance to the single agent develops, sequential administration of other drugs is required. Combined administration of different drugs is also required to prevent resistance and to improve effectiveness. Although no protocols regarding either combined or sequential administration that can extend OS have been defined so far, such administration strategies are anticipated, because several molecular targeted drugs do extend PFS and would be sensible in the real clinical setting. In either case, prospective studies will be necessary in the future.

**Sequential administration**

Sequential administration is a more realistic method, as it would not theoretically require dose reduction and might be able to minimize AE, although there is a possibility of losing the chance of administration at the appropriate timing; that is, when PS is deteriorating. Although reported evidence, such as everolimus administration after VEGFR TKI treatment and sorafenib administration after cytokine therapy are available, established methods for sequential administration of the molecular targeted drugs have not been made so far. Consensus regarding sequential administering methods utilizing different VEGFR TKI has not been established yet. However, retrospective reports showed that sequential methods using sorafenib followed by sunitinib enabled a longer administering period and longer OS than sunitinib followed by sorafenib (61 weeks vs 49 weeks in administering period, and 102 weeks vs 45 weeks in OS). In addition, it is reported that sorafenib is less effective in the case where patients reached PD with sunitinib treatment, therefore the former order might lead to greater clinical benefit. Results of the current prospective studies are awaited. There is currently no reliable evidence regarding administration of a new mTOR inhibitor to patients resistant to other mTOR inhibitors, or evidence regarding administration of VEGFR TKI to patients resistant to mTOR inhibitors.

**Combined administration**

**Concurrent therapy with different cytokine agents (IFN-α + IL-2)**

High ORR of 48.6% and extended OS attained by IFN-α + IL-2 + fluorouracil were reported from foreign countries.

Furthermore, a large-scale RCT carried out by multfacilities comparing IFN-α + IL-2 + fluorouracil concurrent therapy (504 samples) with IFN-α alone (502 patients) was carried out recently. Although there were no significant differences in either OS (18.6 months vs 18.8 months) or PFS (5.5 months vs 5.3 months), both groups obtained 11 CR (durable response in 8 patients with combination therapy and 4 with IFN-α single therapy), and a higher objective response rate was achieved in the combination group (23% vs 16%). High ORR of 38.7% by concurrent therapy of IFN-α + IL-2 was reported in Japan, suggesting that Japanese patients respond better to cytokine therapy in comparison with European and American patients, especially when disease metastasis is limited to the lung. In addition, it was recently reported that some extent of tumor reduction was seen in 81% of patients treated with IFN-α + IL-2. These results suggest that if used in combination, cytokine therapy can be useful, even in the age of molecular targeted therapy.

**Concurrent therapy with molecular targeted agents and cytokine agents**

It is thought that controlling angiogenesis plays an important role for the antitumor effect of oral multikinase inhibitors targeting VEGFR. In addition, it is thought that controlling tumor cell proliferation plays an important role for the antitumor effect of the mTOR inhibitors. In contrast, although the direct antitumor effect to cancer cells is also a part of the action mechanism of immunotherapy, particularly in the case of IFN-α, it is thought that the central mechanism of the antitumor effect of cytokines is an indirect effect mediated by immune cells, such as T-lymphocytes and natural killer cells. Therefore, a synergistic or an additive effect instead of a conflict between molecular targeted agents and cytokine agents can be anticipated when both are used together. Indeed, significantly extended PFS was reported in two double-blind phase III RCT with bevacizumab + IFN-α as compared with placebo + IFN-α in the first-line setting treatment of MRCC. The concurrent therapy with bevacizumab + IFN-α was especially effective in low and intermediate risk groups. Furthermore, concurrent therapy with sorafenib + IFN-α has been reported to be tolerable and effective, and a prospective study with sorafenib + IFN-α is currently ongoing in Japan.

**Concurrent therapy with different molecular targeted agents**

The approach of concurrent therapy with different molecular targeted agents can be divided roughly into two different treatment concepts. One is “horizontal blockade” that targets different signal pathways (e.g. PDGFR, VEGFR and EGFR), and the other is “vertical blockade” that targets the...
same pathway (e.g. HIF-VEGF-VEGFR; Fig. 3),57,58 Some small-scale phase I trials of “vertical blockade” has been reported, but no evidence has been established so far that clearly shows the utility of the “vertical blockade” approach. “Horizontal blockade” raises therapeutic efficiency by blocking different sites on different pathways simultaneously (Fig. 4).57,58 In the case of blocking the HIF-α signal pathway, various targets exist downstream and in cells with different backgrounds. For instance, EGF signal is aberrantly activated in tumor cells, VEGF signal controls tumor angiogenesis by vascular endothelial cells and PDGF is important for proliferation of pericytes, which is important for supporting tumor blood vessels. It is necessary to block different targets simultaneously to control tumor progression, to block angiogenesis and to promote tumor cell apoptosis on treatment. The first report of “horizontal blockade” was a phase II study by Hainsworth in 2005.59 Combined therapy with bevacizumab + erlotinib was reported to attain greater ORR than single bevacizumab therapy, but a negative result was reported afterwards from a randomized placebo-blinded study carried out by Bukowski in 2007.53 However, it was recently reported that combined therapy with bevacizumab + everolimus was tolerable, even at full dose.60 Although the concurrent therapy with other molecular targeted drugs were often intolerable, it seems that the aforementioned approach can be a choice in the future, because a tolerable combined regimen of the two molecular targeted drugs was actually reported.60

**NCRCC**

Most large-scale clinical trials have been carried out on CCRCC that occupies 70–80% of malignant tumors that arises in the kidney. However, except for the clinical trial of temsirolimus, there is little evidence regarding treatment effect on NCRCC in contrast to CCRCC. Temsirolimus was reported to be more effective than IFN-α in both PFS (4.3 months vs 1.8 months) and OS (11.6 months vs 7 months) in the first-line setting of NCRCC according to the result of the subanalysis of phase III RCT.61 In addition, it was shown that the tumor reduction rate of temsirolimus was greater in NCRCC than in CCRCC (68% vs 59%).62 It was reported that sunitinib was more effective than sorafenib in papillary RCC (11.9 months vs 5.1 month in PFS),62,63 and that sorafenib was more effective than sunitinib in chromophobe RCC.62,63 Instead of the molecular targeted drugs, chemotherapeutic agents, such as platinum agents or gemcitabine, are being applied to more rare types of RCC, such as collecting duct RCC or sarcomatoid differentiated RCC.64,65

**Conclusions**

There are unique and characteristic AE of molecular targeted drugs, such as HFS and thyroid dysfunction for VEGF TKI,7,32,33 and hyperglycemia, infectious diseases and interstitial lung disease for mTOR inhibitors.35,36,43 In addition, as most of the clinical trials of the molecular targeted drugs were carried out in Europe and the USA, AE profiles in Japanese patients are not well understood. Post-marketing surveillance of all samples is obligatory in Japan, and AE profiles in Japanese patients are one of the most important issues that should be examined in such investigations. In contrast, cytokine therapy is being reconsidered because of few CR obtained and as a result of various unexpected AE by molecular targeted treatments. We actually have various molecular targeted drugs available at present, and will have more in the future. Furthermore, we...
anticipate utilizing these drugs in various clinical settings, such as in the presurgical setting, the adjuvant setting, sequential administration and combined administration, in addition to cytokines. Therefore, it seems that more elaborate studies are required to obtain the optimal treatment methods as the number of therapeutic agents are increasing. The number of problems to be solved is also increasing in MRCC treatment in the current state. Therefore, it is necessary to develop the knowledge to maximize the effect of such therapeutic agents to extend OS while maintaining the quality of life of RCC patients.

**Conflict of interest**

None declared.

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