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Molecular Targeted Therapies for Patients with Metastatic Renal Cell Cancer

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Abstract

Major breakthroughs have occurred recently in the knowledge of the genetics and transduction pathways involved in various malignancies, including renal cell cancer (RCC). Novel targeted therapies directed against angiogenesis and the mammalian target of rapamycin (mTOR) pathway is now being developed for the treatment of metastatic RCC. Currently, four anti-angiogenesis agents, (sorafenib, sunitinib, bevacizumab, pazopanib) and two specific inhibitors of the mTOR kinase (temsirolimus and everolimus) are approved by the United States Food and Drug Administration. Moreover, at least three other tyrosine kinase inhibitors (TKI) (axitinib from Pfizer, tivozanib from AVEO Pharmaceuticals, and dovitinib from Novartis) are in advanced stages of clinical trials. Here, we will discuss the molecular targeted agents for RCC patients in clinical trials as well as in clinical practice.

Introduction

Renal cell cancer (RCC) is the most frequently occurring solid lesion within the kidney, and its incidence is currently on the increase [1]. Radical nephrectomy remains the standard and only curative therapy for patients with localized RCC [2,3]. However, at initial diagnosis, one-third of RCC patients exhibit visceral metastasis, and up to half of the remainder eventually develop distant metastases [2,4]. Most RCCs have high levels of expression of the multidrug resistance protein P-glycoprotein and are therefore resistant to cytotoxic chemotherapies [2,4]. For a long time, the only effective therapeutic and preventive agents for distant metastases and local recurrence have been interferon (IFN) and interleukin (IL)-2, although these agents have achieved response rates of only 15% [2,3]. Recently, major breakthroughs have occurred in the knowledge of the genetics and transduction pathways involved in various malignancies, including RCC [5]. Novel targeted therapies directed against angiogenesis and the mammalian targets of rapamycin (mTOR) pathway are now being developed for the treatment of metastatic RCC. At the moment, the United States Food and Drug Administration (FDA) has approved four anti-angiogenesis agents: sorafenib (Nexavar; Bayer) [6], sunitinib (Sutent; Pfizer) [7], bevacizumab (Avastin; Genentech/Roche) [8], and pazopanib (Votrient; GlaxoSmithKline) [9]. The FDA has also approved two specific inhibitors of the mTOR kinase, temsirolimus (Torisel; Pfizer) [10] and everolimus (Afinitor; Novartis) [11]. Moreover, at least three other tyrosine kinase inhibitors (TKI) (Axitinib Pfizer; Tivozanib, AVEO Pharmaceuticals; and Dovitinib, Novartis) have reached advanced stages of clinical trials [12]. Here, we describe the molecular targeted agents for RCC patients in clinical trials as well as in clinical practice.

Approved molecular targeted agents and their clinical trials

At first, we describe the clinical efficacy of the six agents currently approved by the FDA. These include four anti-angiogenesis agents, among which sorafenib, sunitinib, and pazopanib are TKI, whereas bevacizumab is a humanized monoclonal antibody that inhibits VEGF-A. The two mTOR inhibitors are temsirolimus and everolimus. The clinical studies mentioned here are summarized in Table 1.

Sorafenib: Sorafenib, an orally active multikinase inhibitor, targets Raf kinase protein; VEGF receptors (VEGFR)-1, 2, and 3; platelet-derived growth factor receptor β (PDGFR-β); FMS-like tyrosine kinase 3 (Flt-3); c-Kit protein (c-Kit); and RET receptor tyrosine kinases [6]. Sorafenib is the first molecular agent targeted at metastatic RCC, demonstrating prolonged progression-free survival (PFS) compared with placebo in patients with advanced cytokine-refractory RCC (n=903) in the phase III clinical study known as Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET) [6]. In TARGET, the median PFS was significantly longer (5.5 months) in the sorafenib group than in the placebo group (2.8 month) [6]. Partial responses were reported as the best response in 10% of patients receiving sorafenib and in 2% of those receiving placebo (P<0.001) [6]. The final overall survival (OS) of patients receiving sorafenib was comparable with that of patients receiving placebo (17.8 v 15.2 months, P=0.146); however, when post-cross-over placebo survival data were censored, the difference became significant (17.8 v 14.3 months, respectively; P=0.029) [13]. Diarrhea, rash, fatigue, and hand-foot syndrome (HFS) were the most common adverse events (AE) associated with sorafenib [6]. These AEs are commonly mild and easily manageable as compared with standard chemotherapies. However, as we reported previously, sorafenib-associated erythema multiforme, which is a toxic mucocutaneous disease with significant morbidity and mortality, might not be a rare AE in Japanese patients [14]. In addition, from a recent phase II dose escalation study of sorafenib, a half of patients (3/6) could be benefitted with PFS of more than 3 months from the escalated dose (600 mg twice a day) due to early progression [15].

Sunitinib: Sunitinib, which is the best available in the United States (Research from the Synovate Healthcare US Tandem Oncology Monitor 2007–2010) for patients with RCC, is an orally administered multi-targeted tyrosine kinase inhibitor [5]. The main targets of sunitinib are VEGF receptors-1-3 and PDGFRs-α and –β [7]. A randomized multicenter phase III trial was conducted enrolling 750 patients with treatment-naive, metastatic RCC to receive either

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Agent	Patients	Number	Control	PFS (months)	probability	OS (months)	probability	US-FDA approval	References
sorafenib	cytokine refractory	903	placebo	5.5 vs 2.8	<0.01	17.8 vs 15.2	0.146	approved	6, 15
sunitinib	treatment naïve	750	interferon	11 vs 5	<0.001	26.4 vs 21.8	0.051	approved	7, 17
bevacizumab	treatment naïve treatment naïve or cytokine	649	interferon	10.2 vs 5.4	0.0001	23.3 vs 21.3	0.336	approved	8, 18
pazopanib	refractory	435	placebo	9.2 vs 4.2	<0.001	ND		approved	9
temsirolimus	treatment naïve	625	interferon	3.8 vs 1.9	<0.001	10.9 vs 7.3	0.008	approved	10
everolimus	TKI refractory	410	placebo	4.0 vs 1.9	<0.0001	14.8 vs 14.4	0.162	approved	11,19
axitinib	cytokine or TKI refractory treatment naïve or cytokine	723	sorafenib	6.7 vs 4.7	<0.0001	ND		approved	22
tivozanib	refractory		sorafenib	ND		ND		not yet	24
dovitinib	TKI and mTOR refractory		sorafenib	ND		ND		not yet	

PFS: median progression free survival (agents versus control), OS: median overall survival (agents versus control), US-FDA: the United States Food and Drug Administration, TKI: tyrosine kinase inhibitor, mTOR: mammalian target of rapamycin

Table 1: Summary of the results of phase III clinical trials of molecular targeted agents for patients with metastatic renal cell cancer.

repeated 6-week cycles of sunitinib (at a dose of 50 mg given orally once daily for 4 weeks, followed by 2 weeks without treatment) or IFN-α (at a dose of 9 MU given subcutaneously three times weekly) [7]. Median PFS was 11 months for sunitinib compared with 5 months for IFN-α ($P = 0.001$) [7]. As cross-over was allowed in this study, the final report showed that median OS tended to be longer in the sunitinib group than in the IFN-α group (26.4 *vs* 21.8 months, respectively, $P = 0.051$) [16]. The objective response rate was 47% for sunitinib compared with 12% for IFN-α ($P = 0.001$) [7,16]. In addition, an exploratory analysis, which censored the 25 patients from the IFN-α group who had crossed over to receive sunitinib, showed a median overall survival time of 26.4 months for the sunitinib group compared with 20.0 months for the IFN-α group ($P= 0.036$) [16]. The AEs were controllable, with the most commonly reported sunitinib-related grade 3 AEs being hypertension (12%), fatigue (11%), diarrhea (9%), and HFS (9%) [7,16].

Bevacizumab: Bevacizumab is a humanized monoclonal antibody that inhibits VEGF. In Europe, a multicenter, randomized, double-blind, phase III trial was conducted of the combination of bevacizumab and IFN-α compared with IFN-α alone for 649 metastatic RCC patients [8]. Median duration of PFS was significantly longer in the bevacizumab plus IFN-α group than that in IFN alone (10.2 months *vs* 5.4 months, $P=0.0001$). Increases in PFS were seen with bevacizumab plus IFN-α, irrespective of risk group or whether reduced-dose IFN-α was received [8]. However, median OS was not significantly different (23.3 months with bevacizumab plus IFN and 21.3 months with IFN plus placebo). The authors commented that patients (> 55%) in both arms received at least one post-protocol anti-neoplastic therapy, possibly confounding the OS analysis [17]. The most commonly reported grade 3 or worse AEs were fatigue (40 [12%] patients in the bevacizumab group *vs* 25 [8%] in the IFN-alone group) and asthenia (34 [10%] *vs*20 [7%]) [8].

Pazopanib: Pazopanib is a second-generation oral angiogenesis inhibitor targeting VEGFRs-1-3, PDGFRs-α and β, and c-Kit [9]. An international randomized, double-blind, placebo-controlled phase III study evaluated the efficacy and safety of pazopanib in treatment-naive and cytokine-pretreated patients with metastatic RCC (n=435) [9]. PFS was significantly prolonged with pazopanib compared with placebo in the overall study population (median, PFS 9.2 v 4.2 months, $P<0.0001$), the treatment-naive subpopulation (median PFS 11.1 v 2.8 months, $P<0.0001$), and the Cytokine-pretreated subpopulation (median PFS, 7.4 v 4.2 months, $P<0.001$) [9]. The objective response rate was 30% with pazopanib compared with 3% with placebo ($P<0.001$) [9]. It is remarkable that no clinically important differences in quality of life were reported for pazopanib versus placebo [9]. Due to these efficacy and safety profiles, the FDA approved pazopanib in 2009, the sixth molecular targeted drug to be approved for metastatic RCC. Currently, an international randomized, phase III study is underway to evaluate the efficacy and safety of pazopanib compared with sunitinib in treatment-naive patients with metastatic RCC.

Temsirolimus: mTOR is a serine/threonine protein kinase that regulates cell growth, cell proliferation, and cell motility. mTOR belongs to the phosphatidylinositol 3-kinase-related kinase protein family and play important roles in survival and growth of cancer cells; thus, it is considered to be a target of molecular targeted agents. Temsirolimus is an intravenously administered mTOR inhibitor. A multicenter, randomized, phase III clinical trial was conducted for 626 patients with previously untreated, poor-prognosis metastatic RCC [10]. In this trial, median overall survival times in the IFN group, the temsirolimus group, and the IFN and temsirolimus combination-therapy group were 7.3, 10.9, and 8.4 months, respectively [10]. The patients who received temsirolimus alone had longer OS ($P = 0.008$) and PFS ($P<0.001$) than did patients who received IFN alone [10]. Rash, peripheral edema, hyperglycemia, and hyperlipidemia were more common in the temsirolimus group, but there were still fewer patients with serious AEs in the temsirolimus group than in the IFN group ($P=0.02$) [10]. In this study, interstitial lung disease was found to be a rare AE [10]. However, nowadays in clinical practice, interstitial lung disease is the most serious AE for the agents of this category, which includes temsirolimus and everolimus.

Everolimus: Everolimus is another oral-administered mTOR inhibitor. The RECORD-1 (*Re*nal *C*ell cancer treatment with *O*ral *R*AD001 given *D*aily) trial was an international phase III, randomized, double-blind, placebo-controlled trial in patients with metastatic RCC (n=410) whose disease had progressed on VEGF-targeted therapy [11]. In this study, a significant difference in efficacy was observed between arms, and the trial was halted early after 191 progression events had occurred (median PFS 4.0 for the everolimus group *vs* 1.9 months for the placebo group, $P<0.0001$) [11]. As 80% of patients in the placebo arm crossed over to everolimus, the median OS differed very little, 14.8 months (everolimus) versus 14.4 months (placebo) ($P=0.162$) [18]. Although stomatitis and rash were the most commonly reported AEs, they were mostly mild or moderate. Interstitial lung disease was the most important AE, detected in 22 (8%) patients in the everolimus group, of whom eight had pneumonitis of grade 3 severity [11]. Everolimus is the first agent to show significant benefit for metastatic RCC patients

after approved targeted therapies such as sunitinib and sorafenib have failed. In addition, currently, treatment of mTOR inhibitor-refractory remains largely undefined. Recently, Grunwald reported on 40 patients who received sunitinib (n=19), sorafenib (n=8), dovitinib (n=10) or Bevacizumab/interferon (n=3) after failure of everolimus. Median PFS, OS, and RR were 5.5 months (range 0.4–22.3) 11.3 months (range 0.8–22.3) and 10% (n=4). From their results, anti-angiogenesis agents might be attractive in everolimus-resistant metastatic RCC [19].

Investigating new drugs

In this section, we report recent advances in the development of second-generation VEGFR TKIs, axitinib, tivozatinib, linifanib, and dovitinb, focusing on their potential benefits of improved potency and selectivity. The former three agents are potent selective inhibitor of VEGFR, whereas the latter targets not only VEGFRs but also Fibroblast growth factor receptor (FGFR).

Axitinib: Axitinib is an oral, potent, and highly selective tyrosine kinase inhibitor among the known VEGFRs, with lower potency against PDGFR and c-kit [20]. In an initial phase II clinical trial for 52 patients with cytokine-refractory metastatic RCC, axitinib demonstrated clinical activity with two complete and 21 partial responses (objective response rate (ORR): 44.2%, 95% CI 30.5-58.7) [20]. In addition, 22 patients showed SD for longer than 8 weeks, including 13 patients with stable disease for 24 weeks or longer [20]. Median PFS was 15.7 months (8.4-23.4, range 0.03-31.5) and median OS was 29.9 months (20.3-not estimable; range 2.4-35.8) [19]. Although 28 patients had grade 3 or grade 4 treatment-related AEs, these AEs were generally manageable and controlled by dose modification or supportive care, or both [20]. After the hopeful results of the phase II clinical trial for patients with sorafenib-refractory metastatic RCC [21], a randomized, open-label, phase III trial compared the efficacy and safety of axitinib versus sorafenib as second-line therapy for metastatic RCC. In this study, 723 patients were randomized to either axitinib (n=361) or sorafenib (n=362), with axitinib demonstrating a significantly longer PFS (medianPFS: 6.7 months for axitinib vs 4.7 months for sorafenib, $P<0.0001$) and higher objective response rate (19.4% for axitinib vs 9.4% for sorafenib, $P=0.0001$) with an acceptable safety profile [22]. In a recent Japanese phase II study of axitinib for the patients with cytokine-refractory metastatic RCC, axitinib also demonstrated significant efficacy for metastatic RCC and was well tolerated in this population. In addition, preliminary findings from this population suggested that baseline proteinuria and soluble VEGFR-2 levels might be key indicators for axitinib-induced proteinuria and efficacy, respectively [23]. To obtain approval as the seventh agent for metastatic RCC, axitinib has been submitted to the FDA and the Japanese Ministry of Health, Labour and Welfare.

Tivozanib: Tivozanib is a potent selective inhibitor of VEGFR-1, 2, and 3 kinases (IC50 0.21, 0.16 and 0.24 nM respectively), and inhibits c-Kit and PDGFR at 10 times higher concentrations (IC50 1.63 and 1.72 nM respectively) [24]. In a phase II randomized clinical trial of tivozanib (1.5 mg/day; 3 weeks on, 1 week off) in patients with metastatic RCC, 272 patients were enrolled, among whom 53% were treatment naïve, 72% had undergone nephrectomy, and 83% had RCC with a clear cell component [24]. The ORR (complete response [CR] +PR) was 27.2%, SD 60.5% and disease control rate (CR/PR + SD) 87.7%. The most common treatment-related AEs (all grades) were hypertension (42%) and dysphonia (16%) [23]. In this phase II clinical trial, tivozanib was active in RCC, and the AE profile of this agent was consistent with that of a selective VEGFR inhibitor, with minimal off-target toxicities. Based on this favorable antitumor activity and safety profile, a phase III, randomized, controlled global, multicenter trial is currently in progress to compare tivozanib with sorafenib in patients with advanced RCC [25]. In addition, based on the selective VEGFR inhibition and the minimal off-target toxicities, a combination phase I clinical trial of tivozanib and temsirolimus was conducted [26]. Preliminary results indicated that the combination of tivozanib with temsirolimus was well tolerated and showed clinical activity in patients with advanced RCC [26]. The investigators concluded that tivozanib was the first VEGFR TKI that could be combined with temsirolimus at the full dose and schedule of both agents [26].

Linifanib: Linifanib (ABT-869, Abbott Laboratories) is a novel anti-angiogenesis agent, selective for all VEGFR and PDGFR with minimal activity against unrelated receptor tyrosine kinases, cytosolic tyrosine kinases and serine/threonine kinases [27]. The open-label, multicentre, phase II trial of oral linifanib was conducted for the patients with advanced RCC (n=43) who were previously treated with sunitinib. ORR was 13.2% and median PFS and OS were 5.4 months and 14.5 months, respectively [28]. The most common treatment-related AEs were diarrhea (74%), fatigue (74%) and hypertension (66%), and the most common treatment-related Grade 3/4 AE was hypertension (40%) [28]. The investigators concluded that linifanib demonstrated clinically meaningful activity in patients with advanced RCC after sunitinib failure and further investigation is necessary [28].

Dovitinib: Dovitinib is a potent receptor TKI that selectively targets VEGFR, PDGFR, FGFR, c-KIT, RET, and Flt-3. Compared to other TKI agents, dovitinib additionally targets FGFR, whose mediated signal has been reported to be an important escape mechanism of anti-VEGFR therapies [29]. In an early phase I study, maximum tolerated dose (MTD) of dovitinib, which was administered p.o. on a 5-day on/2-day off schedule in a repeated 28-day cycle, was defined as 500 mg/day [29]. In a phase II clinical trial for patients with clear cell metastatic RCC, in patients previously treated with a VEGFR inhibitor and mTOR inhibitor (n=31), the best ORRs per central review included PR, 3 (10%); SD more than 4 months, 13 (42%); PD, 6 (19%); and unknown/not assessed, 4 (13%) [30]. Median PFS and OS in these patients were 6.1 and 10.2 months for this group, respectively [30]. Dovitinib demonstrated encouraging antitumor activity with a well-tolerated safety profile in patients with heavily pretreated metastatic RCC [30]. Based on this favorable profile, a phase III, randomized, controlled, global, multicenter trial is currently in progress to compare dovitinib with sorafenib in patients with RCC previously treated with a VEGFR inhibitor and mTOR inhibitor.

Biomarkers to predict response to targeted therapy and prognosis in metastatic RCC

We previously provided a brief overview of biomarkers for

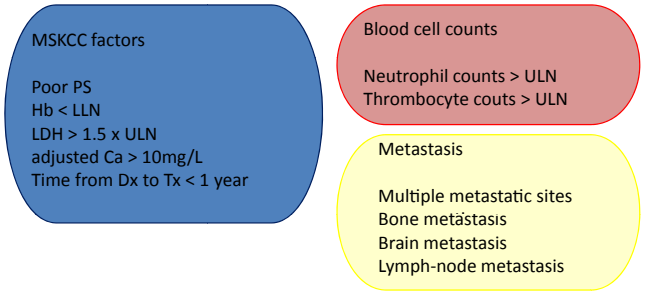

Figure 1: Clinical factors associated with response and/or the survival period of the renal cell cancer patients treated with the targeted agents.

sunitinib and the other targeted agents used in the treatment of metastatic RCC [5]. Regarding clinical factors, the MSKCC prognostic factors, named after the Memorial Sloan Kettering Cancer Center in the cytokine era, include low Karnofsky performance status (PS), high lactate dehydrogenase (LDH), low hemoglobin (Hb), high corrected serum calcium (Ca), and time from initial RCC diagnosis to start of systemic therapy of less than one year, seem to be valid predictors of survival in metastatic RCC [31,32]. In addition to the factors included in the MSKCC score, the number of neutrophils, the platelet count, and the number and/or location of metastatic lesions might be independent prognostic factors in patients treated with molecular targeted agents (Figure 1) [33-35]. The clinical efficacy of sunitinib depends on the systemic exposure of the targeted organ to the active compounds. Orally administered sunitinib is absorbed by the intestinal mucosa and metabolized in the liver. The ATP-binding cassette (ABC) transporter proteins, particularly multidrug resistance 1 [MDR1/ATP binding cassette member B1 (ABCB1), formerly known as P-glycoprotein (P-gp)] and breast cancer resistance protein [BCRP/ATP binding cassette member G2, formerly known as mitoxantrone resistant protein (MXR)], mediate absorption and/or excretion through the intestinal wall and regulate the efflux of a wide variety of anticancer drugs from target cells. These efflux transporter proteins and the cytochrome P450 3A (CYP3A) family play a role in the absorption and metabolism of the agents, respectively [5,36]. The active metabolite and the parent sagents are multi-targeted TKIs that inhibit PDGFR-α and -β; VEGFR-1, -2 and -3; stem cell factor receptor c-Kit; Flt-3 [5,37]. Very recently, Spanish Oncology Genitourinary Group's observational and prospective study demonstrated that two *VEGFR3* missense polymorphisms were associated with reduced PFS with sunitinib and a *CYP3A5*1* high metabolising allele was associated with an increased risk of dose reductions due to toxicity [38]. The efficacy of TKIs can be influenced by multiple genes encoding efflux transporters, metabolizing enzymes, and targeted tyrosine kinases [38-41]. The known adverse effects of the targeted agents include HFS, diarrhea, stomatitis, hypertension, fatigue and hypothyroidism. If AEs depend on the degree of systemic exposure to sunitinib, on which clinical efficacy also depends, AEs may be potential predictors of sunitinib efficacy in metastatic RCC patients. Indeed, these correlations have been reported between clinical response and hypertension, hypothyroidism, and HFS [5,42-44].

Conclusion

In this review, we discussed the approved targeted agents for patients with metastatic RCC and the second-generation targeted agents currently in development. In addition, we briefly reviewed currently reported biomarkers. These targeted agents have been and will likely continue to be used widely for the treatment of RCC. However, several crucial questions remain unanswered. Is any combination of the targeted agents possibly beneficial for patients? How best should these agents be sequenced? Currently we have no answer to either question. We hope that the survival period of patients with metastatic RCC can be prolonged, with a satisfactory quality of life, if we understand how to make optimal use of these targeted agents. We believe that this is our purpose and our mission. Further basic research as well as clinical studies is necessary to reach our goal.

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