Targeted Therapy for Metastatic Renal Cell Carcinoma

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ABSTRAK

Pada sepuluh tahun terakhir, perkembangan terapi target pada karsinoma sel renal bermetastasis menjadi harapan baru dan mampu meningkatkan prognosis penyakit tersebut. Terdapat tiga terapi target yang telah dikembangkan termasuk multi-targeted tyrosine kinase inhibitors (TKI), penghambat mammalian target of rapamycin (mTOR) complex-1 kinase, dan antibodi monoklonal humanized antivascular endothelial growth factor (VEGF). Tujuan artikel ini secara kritis menelaah studi terkini terapi target untuk tatalaksana pasien tersebut. Pada sebagian besar uji klinis yang mengevaluasi terapi target, pasien distratifikasi berdasakan model yang dikembangkan oleh Memorial Sloan Kattering Cancer Center (MSKCC) dan rekomendasi terapi berdasarkan tingkat resiko pasien. Terapi target lini pertama (belum pernah mendapatkan terapi sistemik sebelumnya), sunitinib, pazopanib, atau bevacizumab ditambah IFN-α merupakan pilihan terapi dengan tingkat resiko menguntugkan dan sedang serta gambaran histologi sel jernih. Pasien yang mengalami progresifitas pasca terapi sitokin, sorafenib atau axitinib adalah pilihan yang direkomendasikan. Karsinoma sel ginjal bermetastasis tipe sel jernih dengan tingkat resiko menguntungkan dan sedang yang gagal pada terapi target lini pertama dapat ditatalaksana dengan sorafenib, everolimus, temsirolimus atau axitinib. Akan tetapi, studi saat ini menunjukkan tidak ada pilihan terapi sekuensial terbaik pasca kegagalan terapi lini pertama. Pasien dengan tingkat risiko buruk dan gambaran histologi bukan sel jernih, temsirolimus merupakan terapi target yang didukung oleh uji klinis fase III. Saat ini, beberapa obat baru masih dalam tahap uji klinis fase II dan III dan hasil uji klinis tersebut mungkin dapat mengubah terapi standar pasien karsinoma sel ginjal bermetastasis di masa yang akan datang.

Kata kunci: *karsinoma sel ginjal metastasis, sel jernih, terapi target, terapi sekuensial.*

ABSTRACT

In the past 10 years, recent development of targeted therapy in metastatic renal cell carcinoma (mRCC) has provided a new hope and significantly enhanced the prognosis of the disease. Three class of targeted therapy were developed, including multi-targeted tyrosine kinase inhibitors (TKI), the mammalian target of rapamycin (mTOR) complex-1 kinase inhibitors, and the humanized antivascular endothelial growth factor (VEGF) monoclonal antibody. Hence, the objective of this article was to critically examine the current evidence of targeted therapy treatment for patients with mRCC. In the majority of trials evaluating targeted therapy, patients were stratified according to Memorial Sloan Kattering Cancer Center (MSKCC) risk model and the recommendation of targeted treatment based on risk features. In first-line setting (no previous treatment), sunitinib, pazopanib, or bevacizumab plus IFN-α were recommended as treatment options for patient with favorable- or intermediate- risk features and clear cell histology. Patients who progressed after previous cytokine therapy would have sorafenib or axitinib as treatment options. Clear-cell mRCC with favorable- or intermediate- risk features and failure with first-line TKI therapy might be treated with sorafenib, everolimus, temsirolimus or axitinib. However, the current evidence did

not show the best treatment sequencing after first-line TKI failure. In patients with poor-risk clear-cell and non-clear cell mRCC, temsirolimus was the treatment option supported by phase III clinical trial. In addition, several new drugs, nowadays, are still being investigated and waiting for the result of phase II or III clinical trial, and this might change the standard therapy for mRCC in the future.

Keywords: *clear cell, metastatic, non-clear cell, renal cell carcinoma, sequential therapy targeted therapy.*

INTRODUCTION

Kidney cancer is one of the most common malignancies worldwide with 2% of all adult malignancies, and approximately 271.000 new cases were diagnosed in 2008.[1-3] Approximately 90 % of all renal malignancy are comprised as renal cell carcinoma (RCC).[4] The incidence of renal tumor differs between countries, with the highest incidence in Australia, Europe, and America, and the incidence is low in India, Africa, and China.[5] The mortality was highest in Australia, New Zealand, North America, and Europe, whereas the lowest mortality rate was in Africa and Asia.[2] Over the last two decade until recently, the incidence of RCC increased approximately 2% in Europe and worldwide, though the incidence decreased in Denmark and Sweden.[6] The incidence of kidney cancer in Indonesia is 2.4-3 cases/100.000 population which increased from the earlier estimation approximately 1.4-1.8 cases/100.000 population.[7] Data from Cipto Mangunkusumo hospital between 1995 to 2014, total of 120 patients was diagnosed with RCC. Among them, 28% of patients were present with nodal metastasis and 24% of patients were present with distant metastasis (Mochtar CA, et al, 2015, unpublished data).

Approximately one third of patients diagnosed with RCC present with metastatic diseases, and up to 40% of patients with clinically localized RCC will develop metastasis.[8] Patients with mRCC face a fatal prognosis, with 5-year survival rates less than 10%.[9] In the past 20 years, cytokine therapy using interferon-α (IFN-α) was standard treatment of mRCC and became the main focus of the research for renal cancer. The response rate of mRCC patient treated with IFN-α was less than 10% and median overall survival (OS) was 13 months. In several trials evaluated the cytokine, toxicity frequently occurred and required inpatient administration for intensive care. The limitations of cytokine therapy had intensified the research of a new class of drugs that much more specifics sites of cellular action than immunotherapy. Recent development of more specific action, called targeted therapy, has provided a new hope for the treatment of mRCC and significantly improved the perspective of treatment from this disease.[10]

Three classes of targeted therapy have been developed including multi-targeted tyrosine kinase inhibitors (TKI): sorafenib, axitinib, pazopanib, and sunitinib; the mammalian target of rapamycin (mTOR) complex 1 kinase inhibitors: temsirolimus and everolimus; the humanized antivascular endothelial growth factor (VEGF) monoclonal antibody: bevacizumab with interferon (IFN)-α.[8,11] Abundance of targeted agents has been approved for treatment of mRCC, yet the most effective treatment of mRCC is still unknown. Systemic targeted treatment may be life long and expensive, thus financial reason might be influence the patient compliance.[12] In addition, current Indonesia kidney cancer guideline does not clearly state the targeted treatment strategy for mRCC patient.[13] In order to improve the benefits of the targeted therapy, mRCC patients should be treated based on the risk stratification, histopathology, and status of previous systemic treatment. Hence, the aim of this article is to review the current evidence of targeted treatment and supplements the treatment strategy for mRCC patient in our current guideline.

TARGETED THERAPY FOR METASTATIC CLEAR-CELL RENAL CELL CARCINOMA

Several phase II/III trials evaluated TKI, VEGF monoclonal antibody, and mTOR for treating mRCC patients. These trials predominantly recruited patients with clear-cell RCC histology. Sunitinib, sorafenib, axitinib, pazopanib, bevacizumab+ IFNα were attempted

for clear cell mRCC patients with favorable- or intermediate-risk feature. Temsirolimus was evaluated in phase III clinical trial for poor risk features (**Table 1**).

Table 1. Targeted therapies of clear-cell RCC and their impacts on overall survival (OS) and progression free survival (PFS)

Drug	Dose	Study design	Eligibility	N (patients)	Median PFS (months)	Median OS (months)	References
Compared with IFN- α							
Sunitinib	50 mg/ day orally, 4 weeks-on/ 2 weeks-off	RCT (Sunitinib vs. IFN-α)	- Clear cell mRCC - Without previous systemic therapy - Predominantly favorable- or intermediate- risk	750 (375 vs. 375)	11 vs. 5*	26.4 vs. 21.8	Motzer et al 2009[14,15]
Sorafenib	400 mg twice daily	RCT (Sorafenib vs. IFN-α)	- Predominantly clear cell mRCC - Without previous systemic therapy - Favorable- or intermediate-risk	189 (97 vs. 92)	5.7 vs. 5.6	n.d	Escudier et al 2009[16]
Bevacizumab	10 mg/kg, every 2 weeks intravenous	RCT (IFN-α+Bevacizumab vs. IFN-α+placebo)	- Predominantly clear cell mRCC - Without previous systemic therapy - Predominantly favorable- or intermediate- risk	649 (327 vs. 322)	10.2 vs. 5.4*	23.3 vs. 21.3	Escudier et al 2010[17,18]
		RCT (IFN-α+Bevacizumab vs. IFN-α)	- Predominantly clear cell mRCC - Without previous systemic therapy - Predominantly favorable- or intermediate- risk	732 (369 vs. 363)	8.5 vs. 5.2*	18.3 vs. 17.4	Rini et al 2010[19,20]
Temsirolimus	25 or 15 mg/ weeks intravenous	RCT (Temsirolimus vs. IFN-α)	- Poor risk advanced RCC/ mRCC - Without previous systemic therapy	416 (209 vs. 207)	3.8 vs. 1.9*	10.9 vs 7.3	Hudes et al 2007[21]
Compared with placebo							
Pazopanib	800 mg once daily orally	RCT (Pazopanib vs. placebo)	- Predominantly clear cell advanced/ metastatic RCC - With or without previous systemic therapy - Predominantly favorable- or intermediate-risk	233 (153 vs. 78)	11.1 vs. 2.8*	22.9 vs. 20.5	Sternberg et al 2013[22,23]
Sorafenib	400 mg twice daily orally	RCT (Sorafenib vs. placebo)	- Clear cell mRCC - Favorable- or intermediate- risk - Progressed after cytokine therapy	903 (451 vs. 452)	5.5 vs. 2.8*	17.8 vs. 15.2	Escudier 2009 et al[24,25]
Compared with another TKI							
Pazopanib	800 mg once daily orally	RCT (Pazopanib vs. sunitinib)	- Clear cell mRCC - Without previous systemic therapy	1110 (557 vs. 553)	8.5 vs. 9.5	28.4 vs. 29.3	Motzer et al 2013[22,23]
Axitinib	5 mg twice daily	RCT (Axitinib vs. sorafenib)	- Clear cell mRCC - Progressed after cytokine therapy	251 (126 vs. 125)	12.1 vs. 6.5*	29.4 vs. 27.8	Rini 2011, Motzer 2013[26,27]

TKI= tyrosine kinase inhibitors; N = number of patients; PFS = progression free survival; OS = overall survival; vs.= versus; RCT = randomized controlled trial; *= statistically significant, n.d = not determined

Patient Risk Stratification

The Prognostic model to predict survival of mRCC patients was important for interpreting and designing a clinical trial. An ideal prognostic model must be easy to use and included the most relevant disease characteristics. There were several prognostic models, which predicted the patient survival and influenced the choice of targeted treatment. Memorial Sloan Kattering Cancer Center (MSKCC) and Groupe Francais d'Immunotherapie were calculated the prognostic model based on the outcome of patient treated with immunotherapy, especially IFN-α and Interleukin-2 (IL-2).[14-16] Since the IFN-α was a considered as a suitable comparator of a new drug , the prognostic model that used for clinical trial should be derived from the population of mRCC patient treated with IFN-α therapy. MSKCC model was the first prognostic model to predict survival of patients in interferon era, and was used in the majority of trials to evaluate the targeted treatment. MSKCC risk system stratified patients with poor-, intermediate-, and favorable-risk categories based on the number of clinical features and laboratories (**Table 2**).[14,15]

Table 2. Memorial sloan kattering cancer center (MSKCC) criteria

Risk factors*	Cut-off point used
Karnofsky performance status	<80
Time from diagnosis to treatment	<12 months
Hemoglobin	<LLN
LDH	>1.5 times ULN
Corrected serum calcium	>10.0 mg/dl (2.4 mmol/L)

*Favorable (low) risk: no risk factors; Intermediate risk: one or two risk factors; Poor (high) risk: three or more risk factors
LDH = lactate dehydrogenase; LLN = lower limit of normal; ULN = upper limit of normal

Targeted Therapy for Favorable-to Intermediate- risk Clear Cell mRCC

First line targeted therapy. Most of the trials recruited patients with favorable- or intermediate- risk group based on MSKCC risk model. Data from 7 randomized controlled trial (RCT) were used to determine the efficacy of five agents as first line therapy i.e sunitinib, pazopanib, sorafenib, axitinib, and bevacizumab + IFNα (**Table 1**). Four of these trials were using IFN-α as comparator, and one trial was using placebo as comparator, and two trials were using another TKI as comparator. The majority of trials included patients without prior systemic therapy. Three trials included the patients with prior systemic immunotherapy using IFN-α or IL-2. Choosing between sunitinib and pazopanib as the first line therapy was still controversial, and two trials were performed to evaluate the efficacy between two agents.

Sunitinib. The first Phase-III trial in 750 showed that patients treated with sunitinib had longer PFS (11 month vs. 5 month) than IFN-α group.[17] Median OS of this study was 26.4 months for sunitinib group and 21.8 months in IFN-α group (HR 0.82, 95% CI 0.67 – 1.00, p= 0.051). Patients included in this study were predominantly favorable (n=264; 35.2%) or intermediate (n=421; 56.1%) according to MSKCC risk features.[17,18] Analysis of large sunitinib global expanded-access study, a population based study that included a total of 4,543 patients from 50 countries treated with sunitinib, showed that median OS was 18.4 months and 19.0 months in the patients with or without prior cytokine therapy, respectively. The median PFS was 9.3 and 9.7 months in the patients with or without prior cytokine therapy.[19] Other cohort study in different population setting showed different median OS with 33.1 months and 17.3 months in the Japan and Canada population.[20,21] Data from RenIs (Renal Information System), a epidemiological database for patients treated with targeted therapy in Czech Republic, showed a small difference of PFS between patient in the population and clinical trials (10 months vs. 11 months).[22]

There are many factors that influence the effects of sunitinib (**Table 3**). The reduction of OS was significantly associated with six factors including Eastern Cooperative Oncology Group (ECOG) performance status >1, time from diagnosis to treatment <1 year, hemoglobin <lower limit of normal (LLN), calcium >upper limit of normal (ULN), neutrophil count >ULN, platelet count >ULN. Grassi et al showed that

Table 3. Factors associated with reduced OS in mRCC patients treated with Sunitinib

Study	Parameters	HR	95% CI
Gore et al (2015)31	ECOG PS >1	2.2	1.98-2.44
	Time from diagnosis to treatment < 1 year	1.32	1.21–1.44
	Hemoglobin < LLN	1.84	1.68–2.01
	Calcium > ULN	1.41	1.25–1.59
	Neutrophil count > ULN	2.03	1.83–2.25
	Platelet count > ULN	1.36	1.23–1.50
Mizayaki et al (2015)33	Poor MSKCC clasification	1.73	n.p
	C-reactive protein ≥1.0mg/dl	2.80	n.p
	Liver metastasis	2.37	n.p
Izzedine et al (2015)36	Hypertension patients treated with angiotensin inhibitors	0.55	0.35-0.86
Motzer et al (2013)39	White race	0.34	0.13-0.88
	Bone metastasis	2.34	1.28-4.29
	Baseline corrected Ca > 10 mg/dl	4.36	1.66-11.44
Patil et al (2010)40	ECOG PS > 1	1.52	1.11-2.09
	Time from diagnosis to treatment < 1 year	1.70	1.25-2.33
	LDH	2.01	1.54–2.62
	Corrected Ca level	1.58	1.30–1.86
	Normal hemoglobin level	0.14	0.04-0.44
	Bone metastasis	1.46	1.08-1.99

HR = hazard ratio; CI = confident interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; LLN = lower limit of normal; ULN = upper limit of normal; Ca = calcium; MSKCC = Memorial Sloan Kattering Cancer Center; n.p = not presented

liver metastasis treated with sunitinib had poor outcome. From a series of patients treated with sunitinib in Japan, C-reactive protein (CRP) ≥1 mg/dl, MSKCC poor calcification, liver metastasis were associated with a decrease of OS.[19,21,23] Izzedine et al showed that OS might improve when mRCC patient with hypertensive disease treated with sunitinib and angiotensin inhibitors.[24]

Another important thing in patient with palliative setting beside OS was health-related quality of life (HRQL). Patient with improvement OS should have improvement quality of life. Analysis from Phase III trial compared sunitinib and IFN-α, the study found that HRQL was significantly better in the sunitinib group than IFN-α group. HRQL was measured by Functional Assessment of Cancer Therapy-Kidney Symptom Index-15 item (FKSI-15) and FKSI Disease-Related Symptoms (FKSI-DRS).[17] Sunitinib had higher Quality Adjusted Life Years (QALYs) compared to IFN-α, 1.99 QALYs vs. 1.33 QALYs. However, the incremental cost for one QALYs was still expensive, approximately $ 52,593 (IDR 734,618,108).[25] When sunitinib was compared to best supportive care (BSC), patient treated with sunitinib had higher QALY than BSC, 1.36 QALYs vs. 0.39 QALYs. For one extra QALY, there was incremental cost approximately €34,196 (IDR 523,280,336) per QALY gained.[26]

Pazopanib. Strernberg et al performed Phase III clinical trial and randomized 435 patients with predominantly favorable- (n=170, 39%) or intermediate- (n=236; 54%) risk factor. This trial included the patients who had or had not been treated with cytokine therapy. The result of this trial showed that patients treated with

pazopanib had longer PFS compared with placebo (median PFS 11.1 vs. 2.8 month). However, pazopanib treatment did not showed a statistically significant improvement in median OS compared with placebo (22.9 months vs. 20.5 months, in pazopanib and placebo arm, respectively). Diarrhea, hypertension, and nausea were the most common adverse effects observed in pazopanib arm.[27,28]

Sorafenib. In Phase II trial, which evaluated sorafenib as first line therapy, patient treated with sorafenib had similar PFS as treated with IFN-α (approximately 5.7 months). Because of this findings, there was not any phase III trial which performed for evaluating sorafenib as the first-line therapy. However, greater numbers of patients showed regression of tumor size in sorafenib arm (68.2% vs. 39.0%).[18] Different result was found when sorafenib was used for patients with unsuccessful cytokine therapy. Sorafenib showed effects on prolongs the median PFS compared to placebo, 5.5 months in sorafenib arm and 2.8 months in placebo arm. There was no statistically significant difference between sorafenib and placebo for prolonged the median OS.[29,30] Propocio et al assessed sorafenib as first line and second line therapy in community setting, and found that the efficacy of sorafenib was generally as good as in clinical trial, especially when sorafenib was used as second line. Patients treated with sorafenib as first line had median OS 17.2 months and the second line had median OS 16.3 months. This study suggested that sorafenib might be used as first line and second line setting, although the result from clinical trial, which assessed sorafenib as first line therapy, showed no difference compared with IFN-α.[31]

Axitinib. Phase III trial evaluated the efficacy of axitinib compared with sorafenib in mRCC patients. In the subgroup analysis of patients who progressed with cytokine therapy, axitinib was statistically significant in prolonged median PFS, 12.1 months in axitinib arm vs. 6.5 months in sorafenib arm, but there was no statistically significant in prolong the OS.[32,33]

Bevacizumab plus IFN-α. There were two trials that evaluated the efficacy of combination bevacizumab +IFN-α compared to IFN-α alone. Rini et al recruited 732 patients who treated with bevacizumab plus IFN-α or IFN-α alone, and found better results for PFS in bevacizumab plus IFN-α group than IFN-α mono-therapy (8.5 vs. 5.2 month). OS between two groups was no statistically different (18.3 vs. 17.4 months).[34] Other trial from Escudier et al showed statistically different of PFS outcome in bevacizumab plus IFN-α arm vs. placebo plus IFN-α (10.2 vs. 5.4 months).[35]

Comparison between first-line therapy. Several studies evaluated the efficacy of targeted therapy compared with IFN-α or placebo, whereas just pazopanib and sunitinib was compared in head-to head trial.[17,28,36,37] Two randomized clinical trial, COMPARZ (Comparing the Efficacy, Safety and Tolerability of Pazopanib versus Sunitinib) and PISCES (Patient Preference Study of Pazopanib versus Sunitinib in Advanced or Metastatic Kidney Cancer) study, had been conducted to determine treatment options between sunitinib and pazopanib as first line targeted therapy. COMPARZ trial showed the non-inferiority comparative effectiveness between pazopanib 800 mg once daily continuing dose and sunitinib once daily dose of 50 mg for 4 weeks followed by 2 weeks without treatment. Disease-progression events developed in 60% of patients (336 of 557) in pazopanib arm and 58% patients (323 of 553) in sunitinib group. The non-inferiority of pazopanib compared with sunitinib are also observed in PFS outcome (median PFS 10.2 months in sunitinib group vs. 10.5 months in pazopanib group).[38] Even tough the survival rate of sunitinib and pazopanib was similar, these agents might be different in the incidence of toxicities that influenced health-related quality-of-life (HRQoL), and this circumstance should be considered in palliative setting. The PISCES study was designed using crossover method to assess patient's preference either pazopanib or sunitinib. This study reported that more patients were prefer using pazopanib (70% of patients) than sunitinib (22%), with HRQoL and safety as independent influencing factors.[39]

Milis et al[40] conducted a meta-analysis of trial to evaluate the effectiveness of targeted therapy by using adjusted indirect comparison. They found the superiority of sunitinib compared

with bevacizumab plus IFN-α (HR 0.75, 95% CI 0.60-0.93, p = 0.001) and sorafenib (HR 0.58, 95% CI 0.38 to 0.36, p = 0.001) to improve the PFS. In addition, there was no difference between bevacizumab and sorafenib in prolong the OS.

Hence, we recommended that sunitinib, pazopanib, and bevacizumab plus IFN-α were used for mRCC patient in first-line setting (no previous systemic treatment). In addition, sorafenib and axitinib were recommended for patient with previous immunotherapy (with IFN-α or IL-2).

Sequential treatment after progressed with first-line therapy. Most patients experienced disease progression with targeted therapy, and sequential therapy with different agents might be clinically benefits. However, choosing the sequence of TKI remained clinical challenge. The rationale of using sequential therapy for treating progressing mRCC was evaluated in several trial including: RECORD-1 (Renal Cell cancer treatment with Oral RAD001 given Daily); INTROSECT (Investigating Torisel As Second-Line Therapy); SWITCH (Efficacy and Safety of Sorafenib Followed by Sunitinib Versus Sunitinib Followed by Sorafenib in the Treatment of First-Line Advanced mRCC); RECORD-3; AXIS (Axitinib as Second-Line Therapy for Metastatic Renal Cell Cancer). (**Table 4**)

RECORD-1 trial. Motzer et al conducted the first randomized trial of sequential targeted therapy in progressing mRCC patients who got targeted therapy with sunitinib or sorafenib. They randomized 416 patients to receive oral everolimus 10 mg per day or placebo. Majority of patients in this study were favorable- or intermediate- risk factors. The main outcome was PFS using RECIST criteria based on radiology evaluation. This study showed a statistically difference of PFS between everolimus arm and placebo arm with median PFS, which was 4.9 months versus 1.9 months respectively (HR 0.33; p<0.001). However, there was no statistically significant difference OS in everolimus and placebo arm. This study concluded the efficacy and safety of everolimus in patients with mRCC after progression of sunitinib or sorafenib.[41]

INTROSECT trial. This trial compared the efficacy of temsirolimus and sorafenib as second line therapy after progression on sunitinib. This study were randomly assigned 512 patients to receive 25 mg once weekly intravenous temsirolimus or oral sorafenib 400 mg twice per day. The trial found that there was no PFS advantage between temsirolimus and sorafenib, with median PFS in temsirolimus arm was 4.3 months compared with 3.9 months in sorafenib arm. However, in OS outcome, there was a significant difference between median OS of sorafenib arm compared to temsirolimus arm, 16.6 months vs. 12.3 months, respectively. The longer OS suggested that the usage of sequence VEGF inhibitor might have benefits in patients with mRCC.[42]

SWITCH trial. This trial was the first prospective phase III-RCT that evaluated the sequential therapy with sorafenib-sunitinib (So-Su) or sunitinib-sorafenib (Su-So) in advanced/mRCC. From the total of 365 patients included in this study, 182 patients were randomly assorted into So-Su arm and 183 patients into Su-So arm. Median first-line PFS showed similarity between two groups, but median second-line PFS was longer in So-Su than Su-So. Total PFS and OS was no difference between to study group. The study concluded that both of treatment options were similarly effective in patients with advanced/mRCC.[43]

RECORD-3 trial. This trial evaluated the sequential therapy with first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus. The total of 471 patients with metastatic clear cell or non-clear cell RCC enrolled in this Phase-II clinical trial, 238 patients randomly assigned into everolimus-sunitinib and 233 patients into sunitinib-everolimus arm. The primary end point of this study was median OS and PFS. The median combined PFS was not statistically different between two arms which the median PFS was 21.1 months for everolimus-sunitinib arm and 25.8 months for sunitinib-everolimus arm (HR 1.3; 95% CI 0.9 – 1.7). There was no statistically difference between two arms for prolonged OS.[44]

AXIS trial. Seven hundred twenty three patients were evaluated after progressed with first line treatment with sunitinib, temsirolimus, cytokines, or bevacizumab plus IFN-α. They

Table 4. Sequential therapies and their impact on metastatic renal cell carcinoma

Clinical Trial	Treatment groups	Study design	Study eligibility	N (patients)	Median PFS (months)	Median OS (months)
RECORD-1[45,46]	Sunitinib/sorafenib-everolimus vs. sunitinib/sorafenib-placebo	Randomized open label study	- Clear-cell mRCC patients - Progressed on sunitinib or sorafenib	410 (272 vs. 138)	4.0 vs. 1.9*	14.8 vs. 14.4
INTROSECT[47]	Sunitinib-temsirolimus vs. sunitinib-sorafenib	Randomized open label study	- Metastatic RCC patients (any histology) - Progressed after sunitinib as first line therapy	512 (259 vs. 253)	4.3 vs. 3.9	12.3 vs. 16.6*
SWITCH[48]	Sorafenib-sunitinib vs. sunitinib-sorafenib	Randomized open label study	- Metastatic RCC (all histology) - No prior systemic therapy	365 (182 vs. 183)	12.5 vs. 14.9† (5.9 vs. 8.5†† → 5.4 vs. 2.8†††)	31.5 vs. 30.2†
RECORD-3[49]	Everolimus-sunitinib vs. sunitinib-everolimus	Randomized open label study	- Metastatic clear cell or non-clear cell RCC - No previous systemic therapy	471 (238 vs. 233)	25.1 vs. 25.8†	22.4 vs. 23.8†
AXIS[26,27]	Sunitinib – axitinib vs. sunitinib - sorafenib	Double blind-RCT	- Metastatic clear-cell RCC - Progressed after sunitinib as first line therapy	389 (94 vs. 195)	4.8 vs. 3.4*	15.2 vs. 16.5
	Bevacizumab – axitinib vs. bevacizumab - sorafenib	Double blind-RCT	- Metastatic clear-cell RCC - Progressed after bevacizumab as first line therapy	59 (29 vs. 30)	4.2 vs. 4.7	14.7 vs. 19.8
	Temsirolimus-axitinib vs. temsirolimus - sorafenib	Double blind-RCT	- Metastatic clear-cell RCC Progressed after temsirolimus as first line therapy	24 (12 vs. 12)	10.1 vs. 5.3	18.0 vs. 8.5

TKI = tyrosine kinase inhibitors; N = number of patients; PFS = progression free survival; OS = overall survival; vs.= versus; RCT = randomized controlled trial; *= statistically significant; †= combined median OS/PFS after first-line and second line †† = median first-line PFS/OS; ††† = median second-line PFS/OS.

compared the axitinib 5 mg twice daily with sorafenib 400 mg twice daily. PFS is the primary end point using RECIST criteria. The secondary outcomes were OS, objective respond rate, and disease progression. Among 723 patients, 361 patients assigned to axitinib arm and 362 patients assigned to sorafenib arm. The median PFS was 6.7 months in axitinib arm compared with 4.7 months in sorafenib arm (HR 0.665; 95% CI 0.544-0.812; one sided p<0.001). Axitinib was superior compared to sorafenib for the PFS in patients with previously treated with sunitinib. There was no difference in OS data, which median OS 20.1 months in axitinib arms and 19.2 months in sorafenib arm (HR: 0.969; 95% CI: 0.800-1.174, p = 0.374). In the subgroup analysis of patients previously treated with sunitinib, bevacizumab, and temsirolimus, the study did not record any statistically significant difference either in sunitinib or axitinib for prolong the OS.[32]

Therefore, according to these trials reviewed, it concluded that any sequential therapy has similar effects on prolong PFS and OS. Sorafenib, everolimus, temsirolimus, and axitinib might be useful for patients who progressed after first line TKI. In addition, axitinib was superior than sorafenib in term of prolonged PFS, but not prolonged OS of patients who progressed after first line targeted treatment.

Targeted Therapy for Poor-risk Metastatic Clear Cell Carcinoma

The efficacy of targeted therapy, especially temsirolimus, in treating mRCC with poor-risk category was evaluated in Phase-III conducted by Hudes et al. They randomly assigned 626 patients to receive 25 mg of intravenous temsirolimus, 3 million U of IFN-α subcutaneous three times weekly, or the combination therapies with 15 mg of temsirolimus weekly plus 6 million U of IFN-α three times weekly. The comparison between temsirolimus mono-therapy and IFN-α mono-therapy illustrated that the OS was statistically significant with median OS 10.9 months in temsirolimus group versus 7.3 months in IFN-α group (HR 0.73, 95% CI: 0.58-0.92, p = 0.008). The combination of temsirolimus and IFN-α did not show a significant improvement of OS and showed a greater risk of toxicity than mono-therapy subgroup. In addition, this study showed the difference of median PFS in the IFN-α, temsirolimus, and combination-therapy: 1.9 month, 3.8 month, and 3.7 months, respectively.[45]

Temsirolimus was better tolerated than IFN-α with the grade 3 and 4 adverse events lower in the temsirolimus group (67%) than in the IFN-α group (78%). Although, grade 3 and 4 metabolic alteration (hypertriglyceridemia, hyperglycemia, and hypokalemia) and cutaneous rash were more common in temsirolimus group compared with IFN-α. Asthenia, pyrexia, and neutropenia were more frequent in the IFN-α group. Treatment discontinuations due to adverse event were lower in temsirolimus group than IFN-α, 7% and 4 % respectively.[45]

Hudes et al[45] is the only one Phase-III randomized clinical trial that evaluated the efficacy of targeted therapy in naïve poor-risk mRCC patients. If temsirolimus cannot be administrated to poor-risk patients, the alternatives of therapy might be answered from Phase-III trial that enrolled limited number of poor-risk patients. In the AVOREN trial assessing efficacy of bevacizumab, the study included 54 patients from 649 patients who classified as poor risk according to MSKCC risk score. Sub-group analysis of patients with poor risk found that there was no significant differences between patients treated with bevacizumab and bevacizumab plus IFN-α (HR: 0.87; 95% CI: 0.48-1.56).[37] The same results was reported from other studies evaluating the sunitinib for patients with poor risk group. There was no significant difference between OS comparing sunitinib and IFN-α (5.3 months in sunitinib vs. 4.0 months in IFN-α; HR 0.660; 95%CI: 0.360-1.207). In conclusion, bevacizumab plus IFN-α or sunitinib might be used for poor-risk mRCC patients when temsirolimus could not be used.[17]

TARGETED THERAPY FOR METASTATIC NON-CLEAR CELL CARCINOMA

Because of diversity in the molecular and genetic basis of non-clear cell type, the trial was performed for clear cell mRCC, might not be extrapolated to other histology type of RCC. There was no current consensus about appropriate first line treatment due to lack of level 1 evidence. Targeted treatment in non-clear cell RCC focused on temsirolimus, everolimus, sorafenib, and sunitinib.

In the ARCC (Advance Renal Cell Carcinoma) trial, temsirolimus was evaluated in 73 patients with mRCC non clear-cell type (37 randomized to temsirolimus and 36 patients to IFN-α arm).[45] This study found that the differences OS between temsirolimus arm and IFN-α arm were 11.6 months and 4.3 months with HR 0.49; 95% CI 0.29-0.85. They also observed that PFS was longer in temsirolimus arm than IFN-α arm with median PFS in temsirolimus arm 7.0 months vs. 1.8 months in IFN-α arm (HR 0.38, 95% CI 0.23-0.62). This study concluded that temsirolimus had clinically benefits compared to IFN-α in non-clear cell histology.[46]

Escudier et al[47] performed phase II trial to evaluate the efficacy of other mTOR inhibitor, everolimus, for treating 92 patients with metastasis non-clear cell RCC. There were 59% of patients receiving everolimus that had non-progressing disease within 6 months. Median OS was 21 months and median PFS was 7.6 months with grade ≥3 adverse events including asthenia (10.9%), fatigue (5.4%), and anemia (5.4%).

The ESPN (Everolimus Versus Sunitinib Prospective Evaluation in Metastatic Non-Clear Cell Renal Cell Carcinoma) trial conducted

by Tannir et al[48] was performed to evaluate the efficacy of everolimus or sunitinib to treat metastatic non-clear RCC. This study was multicenter randomized clinical trial with cross over design and used PFS as primary outcome. The study reported that OS and PFS showed advantage of sunitinib group compared with everolimus (16.2 months vs. 14.9 months; p=0.01, and 6.1 months vs. 4.1 months; p=0.25, respectively).

INVESTIGATIONAL AGENTS

With the advancement of knowledge of the molecular mechanism about RCC, several agents of new-targeted treatment were being developed for improving the survival of mRCC patients.[49,50] Recently, the majority of phase II or phase III clinical trial included VEGF inhibition as mechanism of action to inhibit tumor progression. Resistance to inhibition of VEGF was being suggested as a reason for tumor progression after therapy of VEGF inhibitor, and dual (or multiple) pathway inhibition was being developed for overcoming resistance to VEGF.[51] Lenvatinib, an agent that inhibit both VEGFR and FGFR, has been granted by Food and Drug Administration (FDA) as a potential treatment of advance RCC based on phase II clinical trial conducted by Motzer et al.[52] Lenvatinib monotherapy showed improvement of median PFS by 39% compared with everolimus (HR 0.61; 95% CI 0.38-0.98; p =0.048). OS analysis showed better outcome in the combination of lenvatinib and everolimus compared with everolimus monotherapy.[53]

In the past decade, immunotherapy has been less studied due to the extensive development of VEGF- and mTOR- directed therapy. However, enthusiasm has been directed to immune surveillance due to dramatic response of anti PD-1 antibody in the patient of RCC.[54] Nivolumab was the most extensively studied PD-1 inhibitor in mRCC. Clinical phase II trial showed a promising efficacy of nivolumab in treating mRCC patients with previous anti-angiogenic treatment. We are still waiting for the recent phase III trial which comparing between Nivolumab and everolimus in mRCC patient with previously treated by systemic therapy.[55,56]

Cabozantinib, a TKI with potent activity against MET gene and VEGFR 2 receptors, has showed clinical benefits in patients with advanced clear-cell RCC in a single arm trial. Phase III METEOR (Cabozantinib vs. Everolimus in Subjects With Metastatic Renal Cell Carcinoma) trial evaluated the efficacy of 60 mg cabozantinib compared with 10 mg temsirolimus, yet this trial is still on going.[57] Other, several clinical trials of phase II or III such as AGS-003 (autologous dendritic cell immunotherapy) and MPDL3280A (an engineered anti-PDL1 antibody) are still in progress.[58,59]

CONCLUSION

The development of targeted therapy has significantly improved the perspective of mRCC treatment. Sunitinib, pazopanib, and bevacizumab have demonstrated significant improvement of PFS as a first line targeted therapy in metastatic clear cell type RCC patients with favorable- and intermediate- risk category. Clear cell mRCC patients with favorable- and intermediate-risk category who progressed after prior cytokine therapy, sorafenib, axitinib, and pazopanib showed improvement of PFS. There was no difference on prolonged PFS and OS between sequential therapies. Temsirolimus showed benefit in prolonged PFS and OS in clear-cell poor risk category and non-clear cell mRCC. Several new drugs are still being investigated and waiting for the results of phase II or III clinical trial.

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