Management and systemic treatment of clear cell metastatic renal cell carcinoma: BSMO expert panel recommendations

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Almost 30% of patients with renal cell cancer present initially with advanced stage IV disease. In the past decade, the management of the metastatic renal cell cancer has been revolutionised by the knowledge of its molecular biology and development of targets against vascular endothelial growth factor and mammalian target of rapamycin pathways. In this paper we present recommendations based on a thorough review of available guidelines and data from the phase III randomised controlled trials that evaluated new agents in patients with advanced metastatic renal cancer.

(Belg J Med Oncol 2015;9(1):16-24)

Introduction

The Belgian Society of Medical Oncology (BSMO) Renal Cancer Task Force Group has prepared these expert panel recommendations to provide oncologists with current evidence-based management of metastatic renal cell cancer and to incorporate the new molecular-targeted therapies in clinical daily practice.

Epidemiology

Based on the data from the Belgian Cancer Registry, on the incidence of kidney cancer in Belgium, there were 981 males and 551 females (total 1,532) diagnosed with renal cell carcinoma (RCC) in 2010. Kidney cancer was the seventh most frequent tumour in males (2.9% of cancer diagnoses) and the tenth most frequent

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: metastatic renal cancer, recommendations, treatment.

Acknowledgment: Special thanks to the BSMO Board for facilitating this work and to the VUB for the venue.

tumour in females (2%). RCC was diagnosed at a mean age of 64 years in males and 66 years in females.[1]
In 2008, the age-standardised kidney cancer incidence and mortality per 100 000 in Belgium were estimated at 15.8 for males and 7.1 for females, and 6.5 for males and 2.7 for females, respectively. While, across the European Union, incidence/mortality ratio among males raged from 6.9/2.5 per 100 000 in Cyprus to 33.6/12.6 per 100 000 in Czech Republic.[2]
Almost 30% of patients with renal cell cancer present with advanced, stage IV disease.[1]
After nephrectomy for earlier stage of RCC, up to 50% of patients develop recurrent or metastatic disease. Eighty-five percent of these recurrences occur within three years after initial resection, however relapse can develop even several decades later. The median time to diagnosis of recurrence ranges from fifteen to thirty-two months for pT2 and pT3 tumors.[3,4] Five-year relative survival for kidney cancer is highly dependent on the extent of the disease, ranging from 91% in stage I to around 15% in stage IV disease.[1-4]

Pathology report

Before starting systemic treatment, patients with metastatic RCC (mRCC) should undergo a biopsy either in the primary or metastatic site in order to confirm the clear cell histological type and to determine the tumour grade, unless material is already available from the prior nephrectomy. To maximise the diagnostic yield and minimise morbidity, mainly haemorrhagic complications, 18-gauge needles are recommended. At least two >10 mm in length, non-fragmented cores should be obtained. However, it should be understood that the accuracy of Fuhrman grading is low on biopsies (43-75%). [5-8]

Imaging in clear cell mRCC

Base line imaging

CT-scans of the thorax, abdomen and pelvis remain the gold standard as base line imaging tools. However, patients with clear cell mRCC typically present with one kidney and/or altered renal function. In these cases, IV pre-post CT hydration can be considered, and/or CT abdomen could be replaced by magnetic resonance imaging (MRI).[9] Bone scan or MRI (CT) of the brain are usually only done if clinically indicated.

Response evaluation

The Response Evaluation Criteria in Solid Tumours (RECIST) is the most commonly used international guideline for the evaluation of treatment response in solid tumours and is based on assessing changes in tumour size. RECIST criteria include evaluation of five organs, two lesions per organ, lymph node short axis >15 mm, other lesions >10 mm longest axis, and progressive disease >30% increase in total tumour length. A modified version of RECIST guidelines (RECIST 1.1) has also been introduced.[10,11]
New targeted therapy may cause early/extensive tumour necrosis without marked decrease in size. Size, attenuation, morphology, and structure (SACT and MASS) criteria have been developed recently to improve the assessment of treatment response in clear cell mRCC patients on targeted therapy, however they are not yet validated for use in clinical practice.[12] Thus, RECIST remains the gold standard for response evaluation.

PET/CT role

While ^{18}F-FDG PET/CT has shown promising results in several other tumour types, the excretion of ^{18}F-FDG via the urinary system, its low sensitivity, and high rates of both false positivity and false negativity in primary and mRCC patients limit its use. Recent data have suggested a role of ^{18}F-FDG PET/CT in the response evaluation to TKI.[13,14] However, further studies are needed before the PET/CT can be routinely applied in the care of patients with clear cell mRCC.

Response follow-up

The frequency and duration of follow-up in patients with clear cell mRCC under TKI treatment has not been defined. Patel et al. proposed contrast enhanced computed tomography of thorax, abdomen, and pelvis three months after treatment initiation and every three months thereafter.[15]

Prognostic scoring systems in clear cell mRCC

Original and Modified MSKCC

The most widely used prognostic model is from the Memorial Sloan-Kettering Cancer Centre (MSKCC), which stratifies patients with mRCC into poor-, intermediate-, and favourable-risk categories based on the number of adverse clinical and laboratory parameters present. This model was initially developed in patients undergoing treatment with cytokines (INF).
The original MSKCC data identified patient factors that negatively contribute to outcome, such as elevated lactate dehydrogenase (LDH >1.5 upper limit of

Table 1. Prognostic scoring systems for clear cell mRCC.

	Original MSKCC	Modified MSKCC	IMRDC (Heng's model)	Predictors used to select patients for Temsirolimus
Interval from diagnosis to systemic treatment<1 year		x	x	x
Karnofsky performance < 80%	x	x	x	x
LDH >1.5 x ULN	x	x		x
Corrected calcium > ULN	x	x	x	x
Hb< LLN	x	x	x	x
Absence of prior nephrectomy	x			
PMN< LLN			x	
PLT >ULN			x	
≥Two sites of organ metastases				x
Liver metastasis				

ULN = Upper Limit of Normal; LLN = Lower Limit of Normal. PMN: polymorphonuclear neutrophil. PLT: platelets. MSKCC: Memorial Sloan-Kettering Cancer Center IMRDC: International Metastatic RCC Data Base Consortium.

normal), elevated corrected calcium (>10 mg/dl), poor performance status (Karnofsky Performance status <80%), anaemia (haemoglobin below lower limit of normal), and absence of prior nephrectomy.[16] Modified MSKCC or Motzer criteria include, besides the above-mentioned factors, an interval of less than one year from initial RCC diagnosis to initiation of systemic treatment.[17]

IMRDC or Heng's model

A prognostic model for survival in patients with mRCC treated with vascular endothelial growth factor (VEGF)-targeted therapies has been developed and is known as the International Metastatic RCC Database Consortium (IMRDC) or Heng's model. This model was derived from a retrospective study of 645 patients with mRCC treated with sunitinib, sorafenib, or bevacizumab plus interferon. Additional independent adverse prognostic factors validated in this model are absolute neutrophil count greater than upper limit of normal and platelets greater than upper limit of normal.[1]

Survival in metastatic renal cell carcinoma

The advent of targeted therapies has extended median survival for mRCC. In patients who have no poor prognostic factors median overall survival used to be 20 months in the interferon-α era, but has improved to more than three years with the introduction of VEGF-targeted therapy. Median overall survival of patients with intermediate risk has increased from ten months to 26 months with the use of targeted drugs. Although poor outcomes persist for patients in the poor-risk group, median overall survival has improved from four months with interferon-α to nine months with VEGF inhibitor treatment.[16-18]

Harshman et al. reported that patients with favourable risk at initiation of targeted therapy and alive at eighteen months after start, have a 69% probability of

living an additional two years from the 18-months time point compared with 33% for those with a poor prognosis.[19]

Treatment

Surgery in clear cell mRCC

Radical/cytoreductive nephrectomy

The indication of surgery in clear cell mRCC should always be discussed in a multidisciplinary group. The evidence for cytoreductive nephrectomy before cytokine therapy came from two prospective randomised clinical trials, Southwest Oncology Group (SWOG) 8949 and European Organisation for Research and Treatment of Cancer (EORTC) 30947, which revealed a survival benefit for nephrectomy followed by IFN- compared with IFN-alone (a median survival of 11.1 and 8.1 months, respectively, in the SWOG trial, and seventeen and seven months, respectively, in the EORTC trial). In daily practice, cytoreductive nephrectomy is recommended in patients with a good PS, large and/or symptomatic primary tumor.[20,21]

Additionally, Marcus et al. reported that 4.4% of patients with mRCC had spontaneous regression of metastatic lesions after cytoreductive nephrectomy in the pre-TKI-era.[22]

The role of radical/cytoreductive nephrectomy in the era of targeted therapy is unknown. Recently, Heng et al. reported the results of a study evaluating the role of cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma treated with targeted therapy. The median overall survival of patients with cytoreductive nephrectomy versus without was 20.6 versus 9.5 months ($p<0.0001$). Authors found that cytoreductive nephrectomy can be beneficial even after adjustment for prognostic factors.[23]

Two ongoing prospective studies, CARMENA and SURTIME, are comparing a combination of surgery and sunitinib with sunitinib alone for metastatic kidney cancer. No results are available at present.

Thus, cytoreductive nephrectomy allows for obtaining better tumour specimens for pathology analysis to look for sarcomatoid or other pathological differentiation, which may be relevant for the treatment decision.

Metastasectomy

The rate of single site metastases in renal cell cancer patients is 61% versus 39% for metastases at two or more sites. The most common sites of these lesions are lung (45.2%), bone (29.5%), lymph nodes (21.8%), liver (20.3%), adrenal (8.9%) and brain (8.1%).[24] Complete removal of metastatic lesions contributes to improvement of prognosis. In patients with synchronous metastatic spread, metastasectomy should be performed if the disease is resectable and the patient has a good PS.[25] Retrospective and non-randomised study showed that in patients with limited tumour burden after targeted therapy, metastasectomy is feasible with acceptable morbidity, and that a significant time off targeted therapy and long-term tumour-free status are possible with this approach. Thus, the option of metastasectomy has to be continuously re-evaluated, even with the new treatment modalities.[26]

First-line treatment of clear cell mRCC

Patients with good and intermediate MSKCC prognosis score

Observation as a treatment strategy

RCC can follow an indolent course even when the disease is at an advanced stage. Since systemic treatments for clear cell mRCC are not curative and often toxic, there is an argument for deferring therapy until there is a clinically relevant burden of disease, at which time the side effects of treatment are counterbalanced by relief of symptoms and disease control. Fisher et al, in a retrospective cohort study, evaluated clinical outcome in 62 patients with mRCC, in whom first-line systemic therapy was deliberately deferred. Almost all patients (except one) had favourable or intermediate risk disease, as defined by Heng et al. First-line systemic treatment was deferred by an average of eighteen months and median PFS and OS were comparable to those in the pivotal phase III sunitinib study.[27,28]

Targeted therapy

The approval of sunitinib by FDA and EMA as first-line therapy is based on a phase III trial that compared its efficacy versus IFN in 750 patients with favourable or intermediate risk. The overall response rate (ORR) rate was 47% versus 12% in favour of sunitinib and a significant increase in PFS (11 versus 5 months; HR=0.53; $p<0.001$) was observed, OS was 26.4 versus 21.8 months (HR=0.82; $p=0.051$).[29]

The efficacy of pazopanib was assessed in a phase III trial against placebo as first- or second-line therapy (after treatment with cytokines) in 435 patients with favourable or intermediate prognosis. When the entire patient population was analysed, the pazopanib arm was associated with greater OR (30%) and PFS rates as compared to placebo (9.2 versus 4.2 months;

Recommendation/reimbursement in Belgium for targeted therapy in first-line treatment of clear cell mRCC patients with good and intermediate prognosis score

- **Sunitinib** or **pazopanib**.

Pazopanib non-inferior compared to sunitinib. Different side-effect profiles.

The choice between sunitinib and pazopanib should be based on patient specific characteristics.

- **Bevacizumab plus interferon** an alternative option when sunitinib is not tolerated within the first four weeks of start of treatment.

HR=0.46; 95% CI: 0.34-0.62; p<0.0001). Also when the analysis was limited to patients with no previous therapy (11.1 versus 2.8 months; HR=0.40; 95% CI: 0.27-0.60; p<0.0001) or limited to patients with previous cytokine exposure (7.4 versus 4.2 months; HR=0.54; 95% CI: 0.35-0.84; p<0.001), similar significant differences were observed.[30]

The COMPARZ trial involving 1,110 patients with mRCC showed pazopanib to be non-inferior to sunitinib and to be associated with less hand-foot skin reaction, fatigue, and stomatitis, though more liver function abnormalities and hair colour changes were present with pazopanib. Median PFS was 8.4 months with pazopanib and 9.5 months with sunitinib, a non-significant difference.[31]

The PISCES study compared therapy with pazopanib and sunitinib and evaluated the preference of physicians and patients towards one or another. It was observed that 61% of the physicians and 70% of the patients preferred therapy with pazopanib (versus 22% of preference for sunitinib for both, patients and physicians), p<0.001. The relative absence of fatigue was the main reason for the preference for pazopanib.[32]

The role of bevacizumab was evaluated in two randomised studies including 649 and 732 patients with clear cell mRCC, which compared IFN plus bevacizumab versus IFN alone.[33,34] In both studies, PFS was superior in the IFN-bevacizumab arm compared to IFN alone (in the European study [AVOREN] – 10.2 versus 5.4 months, HR=0.63; 95% CI: 0.52-0.75; p=0.0001; in the North American study – 8.4 versus 4.9 months, HR=0.71; 95% CI: 0.60-0.80; p<0.0001). An exploratory analysis of AVOREN demonstrated that patients whose IFN dose had to be reduced to three or six million units due to side effects maintained benefit from treatment with a better toxicity profile.[33-35]

Recommendation for IL-2 in first-line treatment of clear cell mRCC patients with good and intermediate prognosis score

- High dose IL-2 is an option in young patients who could support the side-effects.
- Chance of durable complete remission (CR in 9.3% of patients, durable in 80% of cases). Only in specialised centre with experience.

Sorafenib may be a first-line option in selected patients. However there are no randomised trials as yet comparing sorafenib with pazopanib, only very recently Michel et al. reported an abstract form the first results of the SWITCH trial. The SWITCH trial was a phase III, prospective study comparing the sequencing of the two treatments in 365 patients with advanced or metastatic renal cell carcinoma. Patients were randomly assigned to sorafenib 400 mg (n = 182) or sunitinib 50 mg (n = 183) and upon progression or intolerable toxicity were switched to the opposite treatment. No statistically significant difference in total progression-free survival and overall survival was found between the two treatment arms, but more patients received second-line therapy in the sorafenib-sunitinib arm.[36]

The choice between sunitinib and pazopanib should be based on patient-specific characteristics and shared-decision making between the physician and the patient.

<u>High dose IL-2 as an option</u>

The National Cancer Institute (NCI) phase II experience in the pre-TKI era with 227 patients treated with high-dose IL-2 IV demonstrated complete response (CR) of 9.3%, partial response (PR) of 9.7% and objective response (OR) of 19% patients. Out of the 21 patients who achieved CR, 17 (81%) maintained it for a long time.[37] Phase II studies conducted by the Cytokine Working Group (CWG) have suggested that lowering the dose of IL-2 might result in fewer durable

Recommendation for first-line treatment of clear cell mRCC patients with poor prognosis score

- Temsirolimus has been shown to be effective in poor prognosis patients.
  - Superior to interferon.
  - No direct comparison with anti-angiogenic therapies.
- Sunitinib or pazopanib as an option.

responses.[38] A randomised phase III study, conducted by McDermott et al. demonstrated greater response rates and greater duration of response with high-dose IL-2 IV in comparison with subcutaneous IL-2 and interferon-alpha (IFN).[39] In this trial grade III and IV toxicities were more common with high dose IL-2. The side effects were mainly hypotension refractory to fluids and pressors, anuria for more than 24 hours, respiratory distress, confusion, sustained ventricular tachycardia or any sign/symptom of myocardial ischemia or myocarditis, and metabolic acidosis.[39] Thus, high dose IL-2 cannot be used in patients with poor performance status, in elderly patients with cardiopulmonary problems or in patients who require steroids (e.g. brain metastases).

Patients with poor prognosis

In the global Advanced Renal Cell Carcinoma (ARCC) phase III trial, Hudes et al. randomised 626 patients with RCC (clear cell and non-clear cell RCC) to receive either temsirolimus alone, temsirolimus plus IFN or IFN alone. This trial predominantly included patients with poor prognosis. Temsirolimus was well tolerated compared with INF and adverse events were seen more frequently in IFN only and IFN plus temsirolimus groups. OS was significantly improved in the temsirolimus arm (10.9 versus 7.3 months) as was median PFS (3.8 versus 1.9 months). Based on this study temsirolimus was approved for poor prognosis mRCC patients in first line.[40]

On the other hand, it has to be noted that in the COMPARZ trial about 20% of patients were of poor prognosis according to the Heng's score. Hence, sunitinib or pazopanib can also be considered in these patients.[31]

Recommendation for second-line treatment of clear cell mRCC

Choice between:

Everolimus or Axitinib
Sorafenib

No recommendation on sequencing choice after first-line failure.

Second-line treatment of clear cell mRCC

The use of everolimus after sunitinib and/or sorafenib failure is based on a randomised phase III trial (RECORD 1) with 416 patients that compared placebo versus everolimus and demonstrated a significant increase in PFS (1.9 versus 4.9 months, HR=0.33; 95% CI: 0.25-0.43; p<0.001). OS was 14.8 months (everolimus) versus 14.4 months (placebo) (HR=0.87; p=0.162). Most patients (80%) in the placebo arm received everolimus at progression.[41] The most

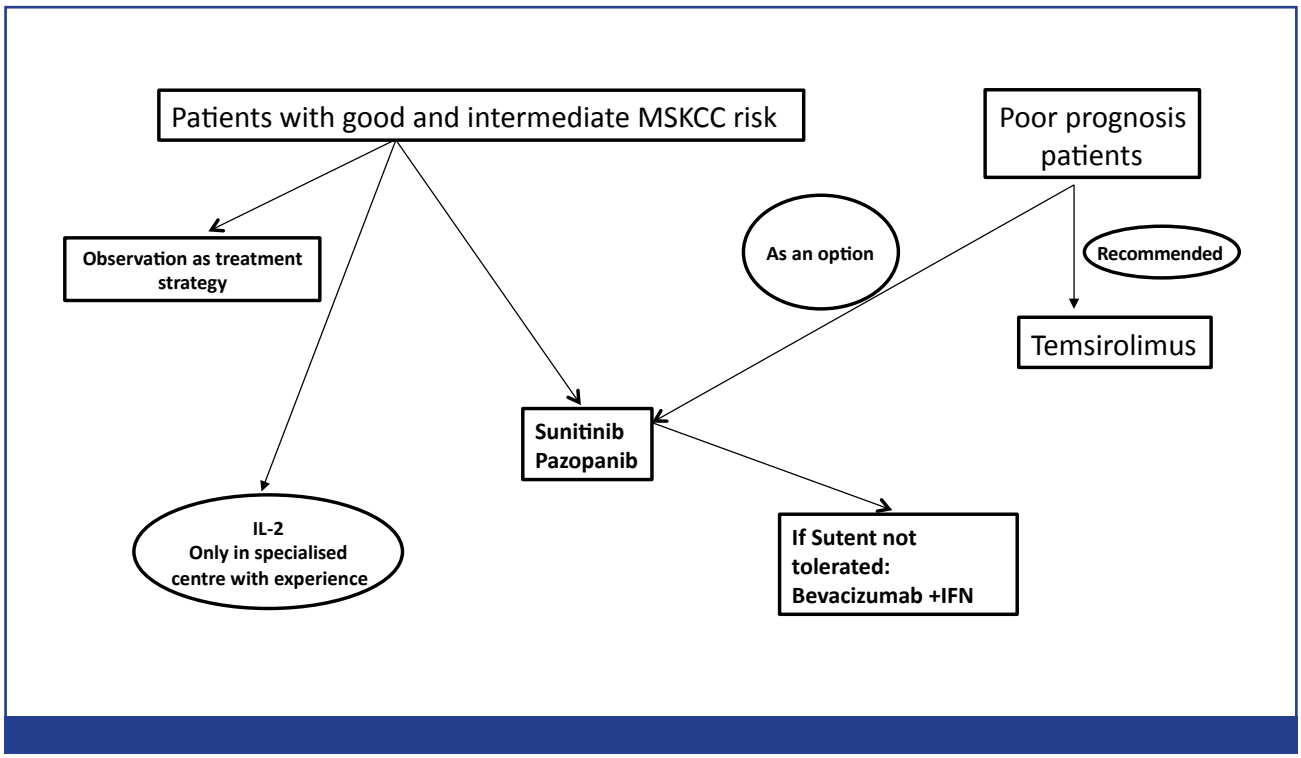

Figure 1. Recommendation for first line treatment of clear cell mRCC.

common side effects in the everolimus arm were stomatitis: 40%, rash: 25%, and fatigue: 20%. It is important to emphasise that pneumonitis of any grade was observed in 8% of the cases, severe in 2.9%. It should also be noted that only 21% of subjects were second-line patients. For most patients the trial was performed in third- and forth-line treatment.[41]

The randomised phase III AXIS trial evaluated the efficacy of axitinib versus sorafenib in patients refractory to first-line therapy with IFN, sunitinib, bevacizumab, or temsirolimus and observed a significant increase in the rates of OR (19.4% versus 9.4%) and PFS (6.7 versus 4.7 months, HR=0.66; 95% CI: 0.54-0.81; p<0.0001) in favour of axitinib. PFS in the subgroup previously treated with immunotherapy (35%) was 12.1 versus 6.5 months (HR=0.46; 95% CI: 0.31-0.67; p<0.0001). The most common grade III/IV side effects with axitinib were fatigue (11%), diarrhoea (11%), and hypertension (16%).[42]

The AXIS trial was conducted in second-line setting only.

Recommendation for third-line treatment and beyond of clear cell mRCC

- Clinical trial when possible.
- Everolimus in patients who have not received it yet.
- Sorafenib as an option.
- BSC should be discussed with frail patients.

In second line setting, in a phase III trial (INTORSECT), 512 patients with mRCC who had progressed first-line therapy with sunitinib were randomised to receive temsirolimus or sorafenib. PFS, the primary end point of the study, was identical in the two arms (4.3 and 3.9 months, respectively). OS, a secondary end point, was significantly longer in patients receiving sorafenib than those receiving temsirolimus (16.6 versus 12.3 months). This longer OS in the sorafenib arm suggests sequenced VEGFR inhibition may benefit patients with mRCC, however according to available data in literature, we cannot give recommendation in favour of one of the available treatment sequencing strategies.[43]

Third-line treatment and beyond

Beyond second-line treatment enrolment into clinical trial is recommended when possible (for running trials consult the www.clinicaltrials.gov website). Everolimus may be considered as an option in third-line setting in clear cell mRCC patients who have not yet received it. In the RECORD 1 trial, the majority of cases were in the third and fourth line treatment. The aforementioned study showed significant increase in PFS compared with placebo.[41]

A recent randomised phase III trial compared sorafenib and dovitinib in the third-line setting in patients previously treated with at least one VEGF-targeted therapy

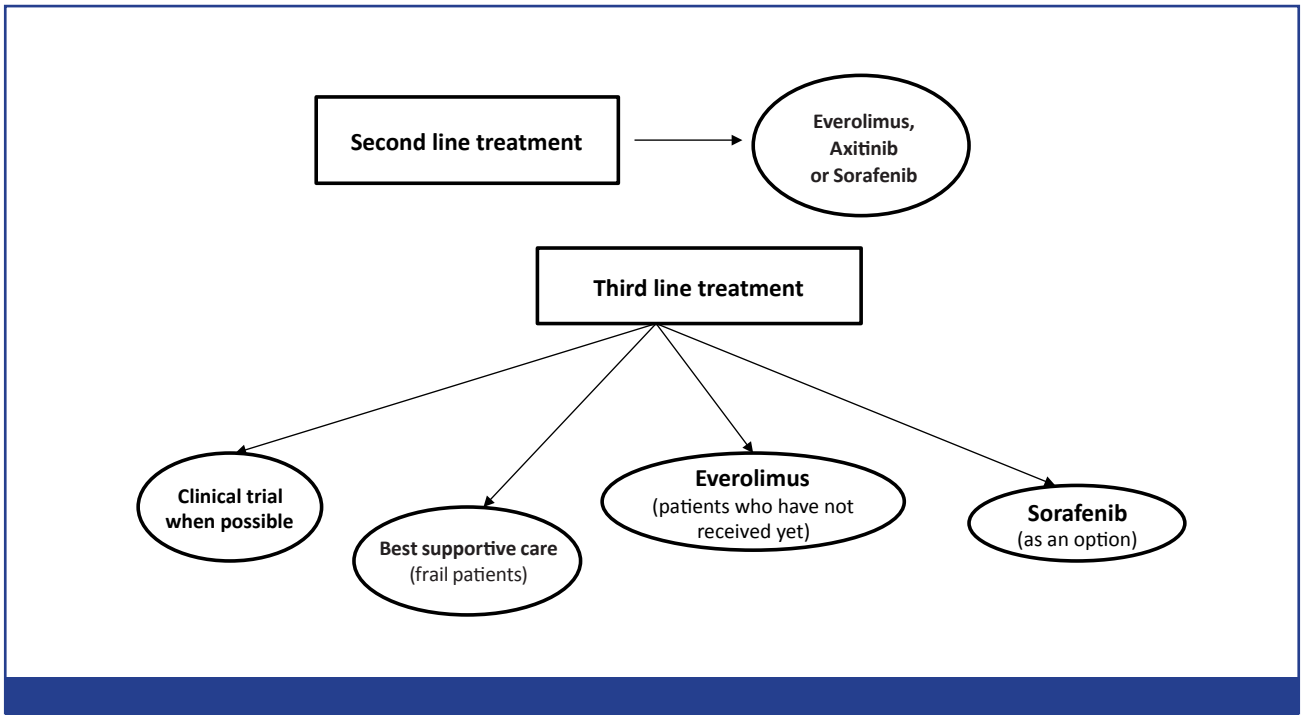

Figure 2. Recommendation for second line treatment and beyond of clear cell mRCC.

(e.g. sunitinib, pazopanib, or bevacizumab) and one mTOR inhibitor (e.g., everolimus or temsirolimus). Dovitinib failed to meet the primary endpoint of improving PFS versus sorafenib. The median PFS was found to be 3.7 months with dovitinib compared with 3.6 months with sorafenib (HR = 0.86; P = 0.063). The median OS was 11.1 and 11.0 months in the dovitinib and sorafenib arms respectively (HR = 0.96; P = 0.357). Very few objective responses (4%) were seen but there was disease stabilisation in about half (52%) of the patients. Based on these data, some authors propose sorafenib (dovitinib is not approved for any indication in USA or Europe) as a third line option in patients with clear cell mRCC.[44]

Best supportive care (BSC) must be considered as an option for frail patients.

Bone and CNS metastases therapy

Bisphosphonate or denosumab can be used for the supportive treatment of bone metastases. Recent evidence favours denosumab to zoledronic acid in preventing skeletal-related events in patients with bone metastases from advanced cancer.[45] Since hypocalcaemia is a possible side-effect of denosumab, calcium and vitamin D supplements should be added unless the patient presented earlier with hypercalcaemia.[45,46]

Radiotherapy can be considered for the treatment of painful bone lesions or spinal cord compression. For the latter, surgery can be an option as well.

For solitary brain metastasis, surgery should be discussed. Stereotactic radiotherapy, if available, is an alternative to surgery for limited volume brain metastases. Whole brain irradiation is recommended for patients with multiple brain metastases.[47] The use of corticosteroids may temporarily relieve central symptoms.

However, there are no randomised controlled trials addressing these questions specifically in renal cell cancer patients and the evidence from the literature in these specific problems is weak.

Conclusion

In this paper we have presented recommendations for the systemic treatment of metastatic clear cell renal cancer. The respective available targeted agents were discussed and recommended sequences of therapy were presented. In addition we summarised the imaging, pathology, cytoreductive nephrectomy and palliative modalities.

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