Systemic therapy for metastatic Renal Cell Carcinoma (mRCC)

HOT SPOT

By Sonal Gandhi, MD, FRCPC, Clinical Fellow, Medical Oncology, Sunnybrook Odette Cancer Centre, and Georg A. Bjarnason, MD, FRCPC, Medical Oncologist and Senior Scientist, Sunnybrook Odette Cancer Centre and University of Toronto

Prognostic factors

- Can dramatically impact the outcome of patients with mRCC and are important to take into account in clinical trial design and the daily care of RCC patients.
- The ***Memorial Sloan Kettering/Motzer prognostic criteria*** were developed based on data from patients treated with Interferon-alpha (INF). Based on functional status, LDH level, hemoglobin level, corrected calcium level and time to relapse, three risk groups were defined: **low risk** (no risk factors, median survival 30 months), **intermediate risk** (one to two risk factors, median survival 14 months), and **high risk** (more than two risk factors, median survival or five months). These criteria have been validated and modified to include prior radiotherapy and multiple sites of metastases as factors and have been used in recent clinical trials.
- **Heng et al.** have developed criteria based on a multivariable analysis of 645 patients treated with sunitinib, sorafenib and bevacizumab that may be more useful today. Based on functional status, hemoglobin level, corrected calcium level and time to relapse, as well as neutrophil and platelet counts, three risk groups were defined: low risk (no risk factors, median survival 37 months), intermediate risk (one to two risk factors, median survival 28.5 months), and high risk (more than two risk factors, median survival or 9.4 months).

Cytoreductive nephrectomy

- Two large trials have shown improved survival with nephrectomy in the setting of metastatic disease in patients treated with INF.
- In a SWOG study, median survival was improved with nephrectomy plus INF versus INF (11 months versus eight months).
- An EORTC study showed a median survival of 17 months with nephrectomy plus INF, versus seven months with INF alone.
- A recent retrospective study (ASCO-GU 2010 abst # 311) in 314 patients (201 had nephrectomy), treated with targeted therapy found that nephrectomy was associated with a median overall survival of 19.8 months as compared to 9.4 months in patients who did not undergo nephrectomy ($p<0.0001$).
- Until proven otherwise, cytoreductive nephrectomy remains the standard of care in eligible, good performance status patients. Prospective trials are ongoing to evaluate cytoreductive nephrectomy in patients treated with TKIs.

Systemic therapy

The current role of systemic therapy in mRCC is summarized in Table 1 based on line of therapy, prognostic group and level of evidence.

- The VEGF (vascular endothelial growth factor) pathway is up regulated in mRCC
- The advent of anti-VEGF therapy has revolutionized systemic treatment for mRCC
- Because of the multiple lines of treatment available post-progression on clinical trial therapies, it has become difficult to obtain survival differences in prospective studies of novel agents. Progression-free survival (PFS) has been found to predict overall survival (OS) in RCC patients and has been accepted as a valid endpoint by regulatory agencies.

First-line Rx

Sunitinib, a TKI inhibitor of VEGF and PDGF, was shown in a large phase III trial to be superior to INF in good- to moderate-risk clear cell RCC. Median overall survival was 26.4 months with sunitinib versus 21.8 months with INF (HR of 0.82, $p=0.051$); progression-free survival was also increased at 11 months versus five months, with an objective response rate of 47% versus 12%.

- Toxicities include hypertension, hand-foot syndrome, diarrhea, fatigue, proteinuria, thyroid dysfunction and, rarely, cardiac dysfunction. Individualized dose/schedule changes can be used to mange most toxicities associated with sunitinib.

Bevacizumab is a monoclonal antibody against VEGF.

- It has been shown in phase II trials to be active as a single agent in metastatic RCC for patients previously treated by immunotherapy.
- The AVOREN trial showed that bevacizumab in combination with INF improves PFS in first-line metastatic renal cell, compared to INF alone: 10.2 versus 5.4 months, HR 0.63, $p=0.0001$), 23-month versus 21-month survival difference (NS).
- The CALGB trial, with an identical design, showed that PFS was improved to 8.5 versus 5.2 months in the bevacizumab plus INF arm, compared to INF alone (HR 0.71, $p<0.0001$). The overall survival endpoint in the combination arm has not yet been reached.
- The adverse effects associated with bevacizumab include asthenia, fatigue, hypertension, proteinuria and, rarely, GI perforation.
- Bevacizumab, in combination with INF, is an option for first-line metastatic RCC.

Table 1.

Treatment Status	Patient Status	Therapy (Level 1 evidence)	Other Options (≥ Level 2)
First Line	Good or intermediate risk	Sunitinib Bevacizumab + INF Pazopanib	High-dose IL-2 Sorafenib Observation Clinical trial
	Poor risk	Temsirolimus	Sunitinib Clinical trial
Second Line	Failed cytokines	Sorafenib Pazopanib	Sunitinib Bevacizumab Axitinib Clinical trial
	Failed VEGFR	Everolimus	Immunotherapy Gem/5FU TKIs Clinical trial
	Failed mTOR inhibitor	Clinical trial	

RCC Treatment Algorithm: 2010

However, it has not been compared head-to-head to other targeted therapies, and bevacizumab is not approved for RCC in Canada.

***Pazopanib*,** another TKI, has been compared to placebo first-line or after one cytokine failure.

- PFS was significantly prolonged with pazopanib compared with placebo in the overall study population (median, PFS 9.2 versus 4.2 months; hazard ratio [HR], 0.46; 95% CI, 0.34 to 0.62; P < .0001), the treatment-naive subpopulation (median PFS 11.1 versus 2.8 months; HR, 0.40; 95% CI, 0.27 to 0.60; P < .0001), and the cytokine-pretreated subpopulation (median PFS, 7.4 versus 4.2 months; HR, 0.54; 95% CI, 0.35 to 0.84; P < .001) [24].
- An ongoing trial is comparing pazopanib to sunitinib first line.

Temsorilmus is an analog of rapamycin, and thus an m-TOR inhibitor.

The m-TOR pathway is another important target in RCC; m-TOR (mammalian target of rapamycin) is a serine/threonine kinase, often upregulated in the P13Kinase/AKT pathway.

Generously supported by an unrestricted educational grant from Novartis

NOVARTIS ONCOLOGY

- A large phase III trial of previously untreated, poor-risk patients with all RCC histologies had improved overall survival compared to INF. Temsirolimus had a median overall survival of 10.9 months versus 7.3 months; HR for death was 0.73, p=0.008. There was no advantage to combining the two therapies.
- Most common side effects were rash, asthenia, peripheral edema, hyperglycemia, hyperlipidemia and lung toxicity.
- Temsirolimus is a reasonable first-line option for patients with a poor performance status due to multiple co-morbidities and/or age. Younger patients whose poor performance status is solely due to extensive mRCC should get sunitinib.
- An ongoing phase III trial is examining temsirolimus versus sorafenib second-line post-sunitinib failure.

- **High dose-IL-2** should be considered for a highly selected group of young healthy patients with clear cell cancer. This is the only therapy that can cure mRCC (in up to seven per cent of patients).

Second-line Rx

Sorafenib has shown efficacy in patients who have previously failed first-line systemic treatment (IL-2 or INF): phase III trial showed improved progression-free survival benefit in patients treated with sorafenib versus placebo (5.5 versus 2.8 months).

- There was no significant overall survival benefit. However, there was crossover from the placebo arm to the sorafenib arm. When this data was censored, the 17-month versus 14-month survival difference became significant.
- Toxicities are similar to that of sunitinib, but there may be less grade 3 or 4 events.
- Sorafenib as first-line therapy has shown similar efficacy as INF in terms of response and PFS.
- Sorafenib can be considered in patients who cannot tolerate sunitinib.

Everolimus is an oral m-TOR inhibitor.

- It is the only targeted treatment thus far with phase III evidence showing benefit second line after progression on TKI therapy.
- Heavily pretreated patients randomized within six months of TKI failure to everolimus versus placebo showed PFS of 4.0 versus 1.9 months with a HR of 0.3 (95% CI: 0.22-0.40Log rank *P* < .0001).
- 60% had stable disease (versus 30% with placebo).
- Everolimus is currently the standard of care for patients who have progressed on sunitinib.

Third- to fourth-line therapy

Interferon

- Two prospective trials have shown a survival benefit for INF, but response rate and duration of response in not as good as for targeted Rx.
- INF can be considered after progression on TKIs and m-TOR drugs.

Chemotherapy

- In general, chemotherapy has shown little efficacy in metastatic RCC with response rates less than 10%.
- Gemcitabine- and 5FU-based regimens may have some activity and can be considered after exhausting targeted treatment and trial options.

Non-clear cell

- Non-clear cell RCC histologies (most commonly papillary and chromophobe) have generally been excluded from the phase III systemic treatment trials (except for the temsirolimus trial abovementioned).
- However, there is mounting evidence to suggest these patients may still benefit from TKI therapy, albeit with less-impressive results. Most of this data is retrospective or from small case series.
- These patients should be considered for relevant clinical trials when possible, until further data in these histologies accumulates.

Adjuvant and neoadjuvant setting

- TKIs can be safely given as neoadjuvant therapy before nephrectomy, but rarely result in significant down-staging of the primary. Currently, neoadjuvant Rx with TKIs should only be done in the context of a clinical trial.
- TKIs are in clinical trials in the adjuvant setting but, to date, there is no evidence for systemic therapy in this setting. Several immunotherapy trials have been negative.

Summary

- VEGF inhibition has greatly improved the outcomes of patients with metastatic RCC. Most of the data is limited to patients with clear cell histology with good or intermediate performance status.
- Sunitinib remains the current reference standard for first-line targeted treatment, particularly for clear cell RCC.
- Everolimus is the only targeted therapy thus far with phase III evidence for second-line treatment after initial TKI failure.
- Ongoing trials seek to identify optimal first- and second-line targeted treatments, and the role of these drugs in neoadjuvant and adjuvant settings.
- Cytoreductive nephrectomy remains the standard of care in good performance status patients with low-volume metastatic RCC.
- There is no active adjuvant therapy available. High-risk patients should be entered on clinical trials.