UK guidelines for the systemic treatment of renal cell carcinoma

There have been recent significant improvements in treatment options for patients with advanced renal cell carcinoma. This article presents UK consensus guidelines on the use of systemic therapies for this poor prognosis disease.

There have been major advances in the systemic treatment options available for patients with renal cell carcinoma over the last few years fuelled by an increasing understanding of the underlying molecular pathways involved in renal cell carcinoma pathogenesis.

These guidelines provide a consensus view about the use of systemic agents for renal cell carcinoma in the UK, on the basis of evidence for clinical utility. Given the speed of advances in the field it is expected that these guidelines will require annual updating for at least the next few years.

Process

A writing committee was convened and produced a draft document which was sent for comment to all lead kidney cancer oncologists for each cancer network in England and Wales. All those who replied and who support the views herein are listed at the end of this article. No responses were received from any clinician stating they did not support this document.

The writing committee elected to use only level I evidence in making firm recommendations. The committee recognizes, however, that there are many areas in clinical practice where there is a lack of level I evidence. Where level II or III evidence exists and can reasonably guide clinical practice this has been stated.

Adjuvant treatment

There is no level I evidence to support the use of any routine adjuvant treatment. No licence exists in the UK for any treatment to be used in the adjuvant setting. Patients at intermediate and high risk of relapse following resection of a primary renal cell carcinoma should be referred to a centre that can offer the possibility of entry into a clinical trial of adjuvant treatment. The current UK National Cancer Research Network adopted adjuvant study is SORCE. Further information can be obtained from the MRC Clinical Trials Unit website (Medical Research Council Clinical Trials Unit, 2008).

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Locally advanced or metastatic disease

Patients with advanced disease should undergo histological review to ascertain the histological sub-type of renal cell carcinoma. They should also be classified according to prognostic group. The most commonly used systems are those described by Motzer that can be applied to either first- (Motzer et al, 1999) or second-line systemic therapy (Motzer et al, 2004).

Immunotherapy: first-line treatment

Interferon-α confers a statistically significant survival advantage in randomized controlled clinical trials and a meta-analysis (level Ia) (Medical Research Council Renal Cancer Collaborators, 1999; Coppin et al, 2000). Increasing evidence shows that patients with intermediate or poor prognosis derive no benefit from interferon-α (Negrier et al, 2007). Given the available data on the first line use of sunitinib (below), the use of interferon-α should at the very least be restricted to good prognosis patients who have small volume disease ideally limited to lung, lymph node and soft tissues.

There are no prospective randomized data demonstrating a statistically significant survival benefit with interleukin-2 (Negrier et al, 2008). However, a small subset of previously untreated patients may derive long-term benefit particularly with the use of high-dose intravenous interleukin-2 (Yang et al, 2003; McDermott et al, 2005). Attempts are being made to identify which patients are most likely to experience greatest benefit (Upton et al, 2005). Treatment with high-dose interleukin-2 can be considered in carefully selected patients, preferably in the context of a clinical trial designed to identify markers that can predict patients who obtain a complete remission.

Targeted therapies: first-line treatment

Sunitinib increased median progression-free survival compared to interferon-α from 5 months to 11 months (hazard ratio=0.42, 95% confidence interval (CI)=0.32–0.54, $P<0.001$) in a population predominantly consisting of good and intermediate prognostic group patients with clear (conventional) renal cell carcinoma (Motzer et al,

2007) (level Ib). Statistical significance was just missed on an intention-to-treat analysis (hazard ratio=0.821, 95% CI=0.673–1.001, *P*=0.051). Many patients crossed over from the interferon-α arm to receive sunitinib or other related therapies upon disease progression. A subset analysis of patients who did not receive second-line treatments showed a doubling of median overall survival from 14 months to 28 months (hazard ratio=0.808, 95% CI=0.661–0.987, *P*=0.0362) (Figlin et al, 2008). Furthermore a subset analysis based on protocol-defined stratification demonstrated that sunitinib was superior to interferon-α in good prognosis patients (*Table 1*).

Bevacizumab in combination with interferon-α increased median progression-free survival from 5.4 to 10.2 months (hazard ratio=0.63, 95% CI=0.52–0.75, *P*=0.0001) in a population of patients with clear cell carcinoma (Escudier et al, 2007a) (level Ib). Only patients in the good and intermediate prognostic groups derived significant benefit from treatment.

In a group of patients considered to have a poor prognosis, 75% of whom were defined as having a poor prognosis by the Motzer system, temsirolimus increased median overall survival from 7.3 months to 10.9 months (hazard ratio=0.73, 95% CI=0.58–0.92, *P*=0.008) in comparison to single agent interferon (Hudes et al, 2007) (level Ib). Combination temsirolimus and interferon-α at lower dose did not have the same effect.

Targeted therapies: second-line treatment post-interferon

Sorafenib extends progression-free survival in good and intermediate prognosis patients with clear cell carcinoma who have progressed following cytokine therapy (Escudier et al, 2007b) (level Ib) (*Table 2*). Progression-free survival was improved from 2.8 months in the placebo group to 5.5 months with sorafenib (hazard ratio=0.44, 95% CI=0.35–0.55, *P*<0.01).

Targeted therapies: second-line treatment post-vascular endothelial growth factor targeted therapy

Everolimus significantly extended progression-free survival compared to placebo (hazard ratio=0.30, 95% CI=0.22–0.40, *P*<0.01) in patients who had progressed after previous treatment with at least one anti-vascular endothelial growth factor therapy (Motzer et al, 2008).

Treatment guidelines based upon level II and III evidence

Level I evidence is not yet available to guide systemic treatment choices in many clinical situations faced by renal cell carcinoma clinicians. This is to be expected in a young and rapidly developing field. However, level II or III evidence is available to guide many scenarios. That which is felt most useful is listed below, but care should be taken in interpreting these data as they are frequently based on small studies, sub-set or retrospective analyses.

Sunitinib following cytokine failure

Phase II studies report a response rate of 40%, median progression-free survival of 8 months and median overall survival of 22 months in good and intermediate prognosis patients with clear cell renal cell carcinoma (Motzer et al, 2006). Sunitinib can be considered as an alternative to sorafenib in patients progressing post-cytokines.

Tyrosine kinase inhibitor following tyrosine kinase inhibitor failure

There is evidence of non-cross-resistance between sorafenib and sunitinib (Tamaskar et al, 2008), and of sunitinib after bevacizumab failure (progression-free survival 30.4 weeks, 95% CI=18.3–36.7 weeks) (Rini et al, 2008). It is therefore reasonable to consider second-line tyrosine kinase inhibitor after first-line tyrosine kinase inhibitor or bevacizumab exposure. Phase III data are awaited to give greater insight into drug sequencing decisions.

High dose intravenous interleukin-2

This regimen produces durable complete responses in around 5% of all patients. It is an intensive and toxic treatment and should be reserved for fit patients who have thorough pre-treatment assessment. It should be restricted to the first-line treatment of patients who have favourable tumour histology and should only be given in centres with appropriate support facilities and experience, preferably within the context of a clinical trial.

Papillary and chromophobe renal cell cancer

Papillary renal cell carcinoma patients were excluded from many registration studies. A total of 73 non-clear cell renal cell carcinoma patients were included in the phase III temsirolimus study, most of whom would have

Table 1. Treatment options based upon level I evidence: first-line treatment for conventional (clear cell) histology

Patient group	First line
Good prognosis	Sunitinib
	Bevacizumab and interferon-α
	Interferon-α
Intermediate prognosis	Sunitinib
	Bevacizumab and interferon-α
Poor prognosis	Temsirolimus

Table 2. Treatment options based upon level I evidence: second-line treatment for conventional (clear cell) histology, good and intermediate prognostic groups

Previous treatment	Second line
Cytokine	Sorafenib
Tyrosine kinase inhibitor or bevacizumab	Everolimus*

*Not yet licensed at the time of publication.

had papillary renal cell carcinoma (Hudes et al, 2007), and they benefited at least as much as patients with clear cell renal cell carcinoma. Thus it is reasonable to consider temsirolimus treatment for patients with non-clear cell carcinoma.

A retrospective report of 41 patients with papillary renal cell carcinoma who received sunitinib or sorafenib described progression-free survival of 11.9 months for those receiving sunitinib (Choueiri et al, 2008) and 5.1 months for those treated with sorafenib. Benefit was also seen in 12 patients with chromophobe histology. Evidence of benefit in non-clear cell histology was also seen in the sunitinib (Gore et al, 2007) and sorafenib (Stadler et al, 2007) expanded access studies. It is therefore reasonable to consider both sunitinib and sorafenib for patients with papillary or chromophobe renal cell carcinoma.

Conclusions

Level I evidence exists for a number of recently developed therapies for the treatment of renal cell carcinoma. This high quality evidence base informs treatment options for many patients with advanced renal cell carcinoma and provides the basis for the treatment recommendations above. Where level I evidence is lacking the available evidence base has been briefly described for a number of common therapeutic scenarios. Level I evidence is expected to shortly be available regarding additional first- and second-line treatment options. **BJHM**

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KEY POINTS

- Therapeutic options for patients with advanced renal cell carcinoma have recently significantly increased.
- High quality evidence for clinical utility is now available for many of the new drugs.
- These UK guidelines make treatment recommendations based upon the currently available level I evidence.
- Guidance is also given for a variety of clinical situations where only level II or III evidence is available.

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