Submission from Cancerbackup to bevacizumab, sorafenib, sunitinib and temsirolimus for renal cell carcinoma

Cancerbackup welcomes the opportunity to contribute to the appraisal of bevacizumab, sorafenib, sunitinib and temsirolimus for renal cell carcinoma. As the leading specialist provider of independent information on all types of cancer, Cancerbackup has regular contact with people living with renal cell carcinoma and those caring for them.

We urge the Appraisal Committee to recommend that bevacizumab, sorafenib, sunitinib and temsirolimus should be available for renal cell carcinoma.

Background

Renal-cell cancer is one of the most resistant of cancers to treatment. The prognosis for people with advanced or metastatic renal cell carcinoma (mRCC) has not improved appreciably over the past 25 years. Up until recently the treatment options for renal cell carcinoma have been very limited. The main treatments have been interferon-alpha or interleukin-2.

Response rates with these treatments are low. Combined data for immunotherapy treatments show an overall chance of partial or complete remission of only 12.4%.[1] The benefits of immunotherapy in terms of overall survival are also very limited. A Cochrane review found that only 8 out of 43 survival comparisons from individual studies demonstrated improved overall survival for immunotherapy over a control. An overall gain in median survival of only 2.8months for interferon alpha compared to controls has been estimated[2].

Recently significant gains in the understanding of renal cell carcinoma have led to the development of new targeted treatments which offer benefits to patients in terms of disease control and quality of life.

The current treatment options

Interferon alpha

The types of interferon used to treat cancer of the kidney is called interferon alpha-2a (Roferon-A®) and interferon alpha-2b (Intron). It is usually given three times a week by subcutaneous injection.

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[1] Coppin C, Porzsolt F, Autenrieth M, Kumpf J, Coldman A, Wilt T. Immunotherapy for advanced renal cell cancer. *Cochrane Database of Systematic Reviews* 2000, Issue 3. Art. No.: CD001425. DOI: 10.1002/14651858.CD001425.pub2

[2] *Ibid.*

Interferon alpha often causes side effects similar to flu symptoms – especially chills, a high temperature, headaches, and aching in the back, joints and muscles. Patients may also have nausea, loss of appetite, depression, autoimmune disorders and tiredness. Interferon has helped some patients with kidney cancer to live longer. The latest data suggest that the only people who benefit are those patients in the good risk group who constitute roughly 20% of people needing treatment for this disease.

Aldesleukin
Aldesleukin is a protein produced naturally in the body in very small amounts. It is produced by a type of white blood cell called a T-lymphocyte. It works as part of the body's defence mechanism (immune system) in fighting illness.

High dose bolus interleukin-2 (IL-2) is rarely used, and has been associated with durable complete remissions in about 10 per cent of patients. However, the widespread use of high dose IL-2 is limited by severe toxicity and the need for specialised care during treatment.

The side effects of aldesleukin may include: flu-like symptoms, nausea and occasional vomiting**,** loss of appetite**,** skin changes**,** tiredness and a general feeling of weakness**,** it may also affect the functioning of the kidneys**,** leading to fluid retention and anaemia. It can also cause changes in the way the heart works and decreased blood pressure.

The therapies under consideration

Sunitinib
Sunitinib is a tyrosine kinase (TK) inhibitor which works by inhibiting a number of important cell signalling pathways, notably the Vascular Endothelial Growth factor (VEGF) pathway. It is licensed for the treatment of people with advanced and/or metastatic renal cell carcinoma and is taken as a tablet.

Some common side effects experienced with sunitinib include: tiredness and a general feeling of weakness, hand-foot skin reaction, sore mouth, effects on the skin and hair, high blood pressure, diarrhoea**,** nausea.

In a phase II trial patients with advanced RCC who had previously had cytokine-based therapy were treated with sunitinib. Of these patients 25 out of 63 (40%) who were given sunitinib had a response to treatment[3]. Of the 25 patients, who responded to treatment, 24 had clear cell histology. This indicates that sunitinib may be particularly effective in this sub group of patients.

A phase III trial of 750 patients with metastatic renal cell carcinoma (mRCC) with clear cell histology was conducted to compare sunitinib to interferon alpha (IFNa). Data from this was presented at ASCO in 2006 and 2007.

Key findings included:

[3] Motzer, RJ, Michaelson, MD, Redman, BG, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, inpatients with metastatic renal cell carcinoma. J Clin Oncol 2006; 24:16

- The objective response rate was significantly increased with sunitinib (39 versus 8 percent with IFNa)[4]
- Median progression-free survival was significantly prolonged (11 versus 5 months)[5].

On average patients in all risk groups for mRCC responded better to sunitinib treatment than to interferon.

Progression-free survival for sunitinib compared to interferon was

- 14.5 months versus 7.9 for those with good risk disease
- 10.6 months versus 3.8 for those at intermediate risk
- 3.7 months versus 1.2 months for those with poor risk disease.

The study found that sunitinib caused a wider range of side-effects than interferon. And, people in the sunitinib group experienced more side-effects than those in the interferon group. However, it is important to note that, measures of quality of life were superior in the sunitinib group. This improved quality of life may have been be due to the greater effectiveness of sunitinib in controlling symptoms of mRCC as well as to the different side effect profiles of the two treatments.

The data available shows that sunitinib has an important role in the initial management of patients with advanced RCC with clear cell histology.

Sorafenib

Sorafenib is a multi-targeted kinase inhibitor. It interferes with the growth of kidney cancer cells. It also works by slowing the growth of new blood vessels within the tumour. It is licensed to treat people with kidney cancer that has spread outside the kidney and who are no longer being helped by treatment with interferon-alpha (IFN) or interleukin-2 (IL-2), or for whom these drugs are not suitable. It is taken as a tablet.

The side effects of sorafenib are generally mild to moderate. Some common side effects are diarrhoea, rash, hair thinning and hand-foot syndrome.

The activity of sorafenib in advanced renal cell carcinoma in previously treated patients was demonstrated in two placebo controlled trials. The results found that treatment with sorafenib was well tolerated and was associated with improvement in disease-related symptoms and in median progression free survival. Unfortunately, due to crossover within one of the trials, it was not possible to say whether overall survival was improved by sorafenib. [6]

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[4] Motzer, RJ, Figlin, RA, Hutson TJ, et al. Sunitininb versus interferon-alfa (IFN-Eo) as first-line treatment of metastatic renal cell carcinoma (MRCC): Updated results and analysis of prognostic factors. (Abstract) J Clin Oncol 2007; 25:241s.

[5] Motzer, RJ, Figlin, RA, Hutson TJ, et al. Sunitininb versus interferon-alfa (IFN-Eo) as first-line treatment of metastatic renal cell carcinoma (MRCC) :Updated results and analysis of prognostic factors. (Abstract) J Clin Oncol 2007; 25:241s.

[6] Escudier, B, Eisen, T, Stadler, WM, et al. Sorafenib in advanced clear-cell renal- cell carcinoma. N Engl J Med 2007; 356:125. and Bukowski, R, Cella, D, Gondek, K, Escudier, B. Effects of sorafenib on symptoms and quality of life: results from a large randomized placebo-controlled study in renal cancer. Am J Clin Oncol 2007; 30:220.

In one phase III trial, 903 patients with advanced RCC of low and intermediate risk, who had not responded to standard therapy, were randomly assigned to sorafenib or placebo[7]. Based upon results at the first planned interim analysis, the study was amended to allow those patients originally assigned to placebo to cross over and receive sorafenib, potentially obscuring differences in survival due to treatment.

This trial demonstrated that sorafenib prolonged disease free survival in patients with low and intermediate risk advanced RCC. The median progression-free survival, was significantly longer in those receiving sorafenib (5.5 versus 2.8 months with placebo).

A final analysis of survival in this trial was presented as ASCO in June 2007[8]. Patients treated with sorafenib had a median survival of 17.8 versus 15.2 months with placebo. While this difference was not statistically significant, almost one-half of the patients originally assigned to placebo had switched to sorafenib, likely obscuring any survival benefit.

Bevacizumab

Bevacizumab is a monoclonal antibody and is given intravenously. It binds to the VEGF neutralising its biological activity. This reduces the ability of RCC to produce blood vessels and so inhibits tumour growth.

Side effects may include high blood pressure**,** allergic reactions, slow wound healing, constipation, circulatory problems, changes in the way the heart works, lowered resistance to infection, bruising or bleeding, damage to the kidneys.

A phase II trial was conducted in 116 patients with advanced RCC, who were refractory to or not eligible for cytokine therapy[9]. Patients were randomly assigned to one of two doses of bevacizumab (3 or 10 mg/kg every two weeks) or placebo. The study was stopped early when an interim analysis disclosed that high-dose bevacizumab was associated with a higher proportion of patients remaining progression free at eight months (30 versus 5%) and significant prolongation in the median time to progression compared to placebo (4.8 versus 2.5 months).

In the phase III AVOREN trial, 648 previously untreated patients were randomly assigned to interferon-alpha alongside bevacizumab or placebo. The bevacizumab or placebo was continued until there was evidence of disease progression.

Key results of this trial included the following:

- The combination of bevacizumab plus IFNa was associated with a statistically significant increase in the response rate (31 versus 13% with IFNa as a single agent).

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[7] Escudier, B, Eisen, T, Stadler, WM, et al. Sorafenib in advanced clear-cell renal- cell carcinoma. N Engl J Med 2007; 356:125.

[8] Bukowski, RM, Eisen, T, Szczylik, C, et al. Final results of the randomized phase III trial of sorafenib in advanced renal cell carcinoma: Survival and biomarker analysis. (Abstract). J Clin Oncol 2007; 25:240s.

[9] Yang, JC, Haworth, L, Sherry, RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med 2003; 349:427.

- The bevacizumab-containing regimen resulted in a statistically significant prolongation of progression free survival (10.2 versus 5.4 months).

Temsirolimus

Temsirolimus is an inhibitor of mammalian target of rapamycin (mTOR) kinase and is given intravenously. The mTOR kinase is involved in intracellular signaling pathways which affect the ability of cells to grow, produce blood vessels and to proliferate.

Temsirolimus has been shown to be of benefit as a first line treatment for people with high risk mRCC. It may be of particular benefit to people with RCC of non-clear cell histology.

A randomised phase II trial has been conducted in refractory patients. When patients were segregated according to prognostic factors for response to IFN-alpha,[10] those with intermediate and poor prognosis disease appeared to benefit the most (median survival 19.3 versus 14 and 8.2 versus 5 months, respectively). Treatment with temsirolimus was generally well tolerated however the most common side effects were maculopapular rash, mucositis, asthenia and nausea (76, 70, 50 and 43 percent respectively).

Based upon the phase II results, temsirolimus was evaluated in a phase III trial in which 626 previously untreated poor prognosis patients with metastatic or recurrent RCC were randomly assigned to temsirolimus, the combination of temsirolimus plus IFNa, or IFNa as monotherapy.

Key results from this trial included the following

- Temsirolimus as a single agent significantly prolonged the median overall survival compared to IFNa as a single agent (10.9 versus 7.3 months)
- Treatment with temsirolimus was better tolerated than either IFNa alone or the combination of IFNa plus temsirolimus.
- In a subset analysis presented at ASCO in 2007, benefit was particularly noted in patients with non-clear cell histology[11].

Conclusion

Cancerbackup believes that NICE should recommend that bevacizumab, sorafenib, sunitinib and temsirolimus should be available for renal cell carcinoma in accordance with their licences for the following reasons:

1. **Bevacizumab, sorafenib, sunitinib and temsirolimus can extend progression-free and overall survival for patients with renal cell carcinoma**
2. **There is evidence that sunitinib can provide better quality of life for patients with advanced renal cell carcinoma**

[10] Motzer, RJ, Bacik, J, Murphy, BA, et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol 2002; 20:289

[11] Dutcher, JP, Szczylik, C, Tannir, R, et al. Correlation of survival with tumor histology, age, and prognostic risk group for previously untreated patients with advanced renal cell carcinoma (adv RCC) receiving temsirolimus (TEMSR) or interferon-alpha (IFN). (Abstract). J Clin Oncol 2007; 25:243s.

3. **Renal cell carcinoma is increasingly recognised to be a heterogeneous disease. The data outlined above shows particular advantages of some of these treatments for specific sub-sets of patients.**

Declaration of interest

Cancerbackup has received sponsorship from Bayer Schering Pharma, Pfizer, Roche and Wyeth for several publications and projects.

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