Research Review
PRODUCT REVIEW

Pazopanib hydrochloride [Votrient®]

About the Reviewer

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This review discusses the evidence in support of the use of pazopanib hydrochloride [Votrient®], an orally administered multi-tyrosine kinase inhibitor (TKI), in the treatment of advanced renal cell carcinoma (RCC). The comparative therapeutic efficacy and tolerability of pazopanib has recently been assessed in three randomised, multicentre, phase III trials.[1-3] Pazopanib has proven efficacy over placebo with respect to progression-free survival (PFS) and objective response rates, and is non-inferior to sunitinib with respect to PFS.[4] Pazopanib has a tolerability profile distinct to that of sunitinib and appears to be superior to sunitinib in many aspects of tolerability and health-related quality of life (QoL).[4] In New Zealand, pazopanib is approved for use in advanced and/or metastatic RCC as first- or second-line therapy in adults. Pazopanib 200 mg and 400 mg film-coated tablets are listed in Section B and Section H of the Pharmaceutical Schedule and are fully funded by Pharmac for use in patients who meet special authority criteria (see: http://www.pharmac.health.nz)

Renal cell carcinoma

Renal cell carcinoma (RCC) is the most common type of kidney cancer, comprising approximately 90% of all renal malignancies, and is the most lethal urologic cancer, with a >40% mortality rate.[5-7] Worldwide, there are approximately 209,000 new cases diagnosed annually and approximately 102,000 individuals die from this disease each year.[8] It is estimated that in 2012, 586 new cases of kidney cancer occurred in New Zealand, and an estimated 198 deaths.[9] International data from 2008 showed renal cancer incidence and mortality rates in New Zealand and Australia to be amongst the highest in the world.[10] The incidence of RCC appears to be higher among Europeans than Asians.[5] The estimated economic burden of metastatic RCC in the US is $107-556 million and interventions to reduce the prevalence of this cancer hold the potential to yield considerable economic benefits.[11,12]

The past years have seen an increase in the mortality rate associated with RCC, however this seems to have peaked and more recently a decline in incidence and mortality has been observed in some Western countries; it is thought that this decline may be associated with a reduction in the incidence of smoking and improved occupational hygiene.[5,8]

The median age at diagnosis of RCC is 65 years and this cancer is 50% more common in men than women.[13] While the aetiology of RCC is unknown, established risk factors include smoking, obesity, germline mutations and advanced kidney disease.[5] There is also some evidence that diet plays a role as does occupational exposure to some known carcinogens.[5] The asymptomatic nature of the majority of small localised RCC tumours results in delayed diagnosis.[14] In fact, approximately 30% of patients present with metastatic disease.[11] For these patients the prognosis is extremely poor.[5]

In RCC, malignant cells are found in the lining of the renal tubules and several subtypes exist; clear-cell (accounting for 60-70% of cases), papillary (5-15%), chromophobic (5-10%), oncocytic (5-10%) and collecting duct (<1%).[15] Among all of the subtypes, stage for stage, clear-cell RCC has the most unfavourable prognosis.[16] The staging system for RCC is based on the degree to which the tumour has spread from the kidney. The American Joint Committee on Cancer has designated staging by TNM (primary Tumour, regional lymph Nodes and distant Metastasis) classification to define RCC.[17] In stage I and II disease, cancer is localised to the kidney, in stage III disease, cancer has spread to the renal or hilar lymph nodes, and in stage IV disease, cancer has spread to adjacent organs (except the adrenal glands), or has metastasised.[17] Stage III and IV disease comprise advanced RCC. The overall estimated average 5-year survival rates for patients with stage I, II, III or IV disease are 96%, 82%, 64% and 23%.[15,18]

A number of prognostic models have been developed to determine outcomes in patients with advanced RCC;[8,19-21] however, there remains a need for robust clinical and biologic features predictive of outcome in patients with metastatic disease.[18]

Treatment options

For localised RCC, nephrectomy is the cornerstone of therapy, although 20 to 30% of patients undergoing surgery experience a recurrence and subsequently develop metastatic disease.[22,23] For metastatic disease, surgery is mostly palliative and systemic therapies are the mainstay.[4] Metastatic RCC generally responds poorly to radiotherapy, hormonal therapy and conventional chemotherapy.[4,14,24] In the past, advanced disease has been treated with interferon-α or interleukin (IL)-2; however, these cytokine therapies have demonstrated a low probability of anti-tumour effect against RCC and their use is often limited by tolerability issues.[4,19]

More recently, therapies targeting vascular endothelial growth factor (VEGF), such as the multi-tyrosine kinase inhibitors (TKIs) pazopanib, sunitinib, sorafenib and axitinib, and the anti-VEGF monoclonal antibody bevacizumab have been developed, as too have the mammalian target of rapamycin (mTOR) protein inhibitors everolimus and temsirolimus.[4] Targeted therapies against the VEGF pathway have extended the lives of those with advanced RCC, with the median overall survival now exceeding 2 years.[25]

ESMO treatment guidelines for advanced RCC

According to the European Society for Medical Oncology (ESMO) clinical practice guidelines for locally advanced RCC, open radical nephrectomy remains the standard of care.[8] For metastatic disease, cytoreductive nephrectomy followed by systemic therapy is recommended for those with a good Karnovsky performance status and large primary tumours,

and for those with symptomatic primary tumours. In some cases, metastasectomy may be appropriate. Radiotherapy may play a useful role in some cases of advanced RCC, as too may bisphosphonate therapy when skeletal metastases are present.[8]

With regard to systemic therapy, the ESMO Guidelines Working Group recommends the agents in the Table below as standard first- and second-line therapy according to histology, setting, and risk group:[8] The European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) have published similar guidelines for the treatment of advanced RCC.[6,26]

Table 1: ESMO Guidelines Working Group recommendations for the treatment of advanced RCC[8]

Histology and setting	Risk group/prior treatment	Drug
Clear-cell; first line	Good or intermediate risk	Pazopanib, sunitinib or bevacizumab + interferon-α
	Poor prognosis	Temsirolimus
Clear-cell; second line	Post-cytokines	Pazopanib, sorafenib, axitinib
	Post-tyrosine kinase inhibitors (TKIs)	Everolimus, axitinib
Non-clear-cell*		Temsirolimus, sunitinib, sorafenib

*The ESMO recommendations for non-clear-cell RCC are based only on the findings of expanded access programs of sunitinib and sorafenib, of small retrospective studies and of the subgroup analysis of the temsirolimus registration trial.

About pazopanib hydrochloride

In New Zealand, pazopanib hydrochloride is indicated for the treatment of advanced and/or metastatic RCC (as first- or second-line therapy in adults) and for the treatment of advanced (unresectable and/or metastatic) soft tissue sarcoma in patients who have received prior chemotherapy (unless contraindicated) including anthracycline treatment.[27]

Pharmacological properties

Pazopanib is a potent multi-TKI that inhibits tumour angiogenesis, cell growth and survival.[4,27] This orally administered agent predominantly targets vascular endothelial growth factor receptor (VEGFR) -1, -2 and -3, platelet-derived growth factor receptor (PDGFR) -α and -β, and the stem cell factor receptor c-Kit.[4,27] As with other licenced kinase inhibitors, pazopanib also targets a number of other kinases, inhibiting fibroblast growth factor receptor (FGFR) -1 and -3, receptor inducible T-cell kinase, IL-2 receptor inducible T-cell kinase, leukocyte-specific protein tyrosine kinase and transmembrane glycoprotein receptor tyrosine kinase.[4]

A study comparing the activity of pazopanib, sunitinib and sorafenib against a large panel of 242 kinases, revealed that pazopanib was more selective than sunitinib, inhibiting a smaller proportion of kinases (12% vs 20%) and showed similar selectivity to sorafenib (11%); however, there were differences against specific kinases.[28] These differences may give rise to the observed differences in the adverse event profiles of these agents.[28]

The mean time to achieve peak concentrations of pazopanib is 2-4 hours and daily dosing results in a 1.23 to 4-fold increase in the AUC.[27] The agent is eliminated slowly with a mean half-life of 30.9 hours following an 800 mg dose.

Dosage and administration

The recommended daily dosage of pazopanib is 800 mg administered in a single dose at least one hour before or two hours after a meal (the administration of pazopanib with a high- or low-fat meal engenders approximately a 2-fold increase in AUC and C_{max}).[27] In order to manage adverse reactions, the dose of pazopanib may be decreased in 200 mg increments in a stepwise fashion based on individual tolerability. Tablets should not be crushed due to the potential for increased bioavailability. Pazopanib is not recommended for use in children and adolescents under 18 years of age. In patients with moderate hepatic impairment, the dose of pazopanib should be reduced to 200 mg/day and the agent should not be used in those with severe hepatic impairment or those on peritoneal dialysis or haemodialysis.[27] Pazopanib is not indicated for use with any other systemic anti-cancer therapies.

Adverse events

The most commonly reported adverse event associated with pazopanib is abnormal liver function, which can occur soon after treatment is initiated.[27] In clinical trials, increases in serum bilirubin and transaminases (ALT and AST) were observed. It is therefore recommended that serum liver tests be undertaken before initiation of treatment and at weeks 3, 5, 7 and 9, and at months 3 and 4, and as clinically indicated, with periodic monitoring continued after 4 months. Simvastatin use concomitantly with pazopanib may increase the risk of ALT elevations.

Hypertension, including hypertensive crises have also occurred in clinical trials of pazopanib and blood pressure should be well controlled before starting the agent. Blood pressure should be monitored frequently. The agent should be discontinued if severe hypertension develops despite antihypertensive therapy or in the case of a hypertensive crisis.

Other reported adverse events include posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome, cardiac dysfunction, QT prolongation and torsade de pointes, arterial thrombotic events, venous thrombotic events, thrombotic microangiography, haemorrhagic events, respiratory disorders, renal urinary disorders, gastrointestinal disorders, skin disorders, weight loss, hypothyroidism, proteinuria and serious infections. Pazopanib may impair fertility in both women and men. There are no adequate data on the use of this agent in pregnancy – the agent should only be used in pregnancy if the potential benefits outweigh any possible risks to the developing fetus.

EXPERT COMMENTARY ON CLINICAL TRIAL EVIDENCE ON THE USE OF PAZOPANIB HYDROCHLORIDE IN THE TREATMENT OF ADVANCED AND/OR METASTATIC RENAL CELL CARCINOMA

Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial[1]

Authors: Sternberg CN et al.

Summary: A randomised, double-blind, placebo-controlled phase III study was conducted to investigate pazopanib monotherapy in 435 patients (233 treatment-naive; 202 cytokine-pretreated) with advanced RCC. Compared to placebo, pazopanib significantly prolonged progression-free survival (PFS) in the overall study population (median PFS 9.2 vs 4.2 months; HR 0.46; 95% CI 0.34-0.62, $p < 0.0001$), and in both the treatment-naive (median PFS 11.1 vs 2.8 months; HR 0.40; 95% CI 0.27-0.60, $p < 0.0001$), and cytokine-pretreated (median PFS 7.4 vs 4.2 months; HR 0.54; 95% CI 0.35-0.84; $p < 0.001$) groups. The pazopanib objective response rate was also increased versus placebo (30% vs 3%; $p < .001$) and the median response duration was >1 year. Common adverse events included diarrhoea, hypertension, hair color changes, anorexia, nausea and vomiting. Clinically important differences in QoL were not observed.

Comment: This is one of the few randomised, placebo controlled studies using a VEGF inhibiting TKI in metastatic RCC. It provides very useful information on the impact of these agents, specifically pazopanib. The primary endpoint of PFS was clearly superior with pazopanib but survival data are still awaited. However, the survival secondary endpoint will be confounded by the fact that 48% of patients receiving placebo subsequently crossed over to pazopanib. More than 90% of study participants had favourable or intermediate risk disease. Both risk groups benefitted from pazopanib as did all other sub-groups.

Despite the initial hope that VEGF inhibiting agents would be relatively non-toxic these drugs certainly have moderate toxicity. In this study hepatotoxicity was the most common toxicity (53%, any grade) and 14% of participants discontinued pazopanib prematurely because of adverse events. QoL assessment is vital in the treatment of metastatic cancer and this was well addressed at multiple time points with the EORTC QLQ-30 and EuroQol-5D instruments. Surprisingly the QoL results were similar in both arms, which raises the issue about the impact of toxic effects in the pazopanib arm.

Pazopanib versus sunitinib in metastatic renal-cell carcinoma[3]

Authors: Motzer RJ et al.

Summary: This randomised controlled phase III trial (COMPARZ) compared pazopanib 800 mg once daily and sunitinib 50 mg once daily for 4 weeks (followed by 2 weeks without treatment) as first-line therapy in 1110 patients with clear-cell, metastatic RCC. Pazopanib was noninferior (predefined noninferiority margin, upper bound of 95% CI <1.25) to sunitinib in PFS (HR for disease progression or all cause mortality 1.05; 95% CI 0.90-1.22). Overall survival did not differ between treatments (HR for death with pazopanib 0.91; 95% CI 0.76-1.08). Those receiving sunitinib had a higher incidence of fatigue (63% vs 55%), hand-foot syndrome (50% vs 29%) and thrombocytopenia (78% vs 41%). In those receiving pazopanib, a higher incidence of increased ALT levels was observed (60% vs 43%). For 11 of 14 health-related QoL domains the mean change from baseline during the first 6 months of treatment favored pazopanib ($p < 0.05$).

Comment: This investigation is the largest direct comparison of pazopanib and sunitinib, the first TKI to be widely used in RCC. The study design was noninferiority and involved first-line treatment in a homogeneous population who largely represented favourable and intermediate risk metastatic disease. The primary endpoint, noninferiority of PFS for pazopanib compared to sunitinib was satisfied.

There was a clear difference in toxicity and QoL profiles. Fatigue and haematological toxicity were problematic with sunitinib and hepatotoxicity with pazopanib. Dose reductions and premature discontinuation of therapy because of adverse events was similar in both arms. The pattern of toxicity from sunitinib was variable between assessment points on day 28 (end of 4 week administration) and day 42 (end of 2 week break from treatment). Anaemia was a feature which may have contributed to fatigue and this was more marked at 42 days whereas neutropaenia was more marked at 28 days. The pattern of toxicities with pazopanib was more even. Although the assessment of toxicity at day 28 could be seen as a potential disadvantage for sunitinib the overall toxicity profiles (including day 28 and 42 data for sunitinib), favoured pazopanib, with the exception of hepatotoxicity. This was reflected in the QoL profiles, including a measure of patient satisfaction.

Overall survival in renal-cell carcinoma with pazopanib versus sunitinb[29]

Authors: Motzer RJ et al.

Summary: This paper reports on the final analysis of overall survival from the phase III noninferiority pazopanib versus sunitinib in metastatic RCC study (presented above). In the trial, overall survival was a secondary endpoint and was defined as time from randomisation to death from any cause. At the time of data cut off, a total of 334 (60%) pazopanib recipients and 335 (61%) sunitinib recipients had died; HR for death with pazopanib vs sunitinib 0.92 (95% CI 0.79-1.06), $p = 0.24$. The median overall survival was also similar between the two groups; 28.3 months with pazopanib and 29.1 months in the sunitinib group. In patients with favourable-risk disease, median overall survival was 42.5 months with pazopanib ($n = 151$) and 43.6 months with sunitinib ($n = 152$); HR for death with pazopanib 0.88 (95% CI 0.63-1.21). In patients with intermediate-risk disease the median overall survival was 26.9 months with pazopanib ($n = 322$) and 26.1 months with sunitinib ($n = 328$); HR for death with pazopanib 0.90 (95% CI 0.74-1.09). In patients with poor-risk disease, median overall survival was 9.9 months among pazopanib recipients ($n = 67$) and 7.7 months among 52 sunitinib recipients; HR for death with pazopanib 0.85 (95% CI 0.56-1.28). The median on-treatment periods for pazopanib and sunitinib were 8.1 months and 7.6 months, respectively. Treatment discontinuation occurred due to disease progression in 56% of pazopanib recipients and in 60% of sunitinib recipients. Adverse events resulting in treatment discontinuation occurred in 24% of pazopanib recipients and 20% of sunitinib recipients.

Comment: Overall survival was a secondary endpoint in this study but is of considerable importance to determine whether there is any obvious difference in efficacy between sunitinib and pazopanib. In particular, could the greater toxicity profile of sunitinib be balanced by better survival? The median overall survival for both agents was approximately 2 years and for the favourable risk subgroup 3.5 years. These are impressive figures and, as in the Sternberg study (above), the outcomes were similar for all sub-groups. The use of second-line TKIs and mTOR inhibitors was similar (around 55%) in both arms and this may have confounded any potential survival advantage from pazopanib or sunitinib. However, this was a non-inferiority design and a clear indication of a survival advantage would require a superiority design, but it is doubtful that such a study will be carried out.

Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES Study[2]

Authors: Escudier B et al.

Summary: A double-blind, randomised, cross-over study evaluated pazopanib or sunitinib patient preferences and the influence on preference of HR-QOL and safety factors in 169 patients with metastatic RCC. Of 114 patients who met pre-specified modified intent-to-treat criteria, 70% preferred pazopanib versus 22% who preferred sunitinib ($p < 0.001$); 8% expressed no preference. All pre-planned sensitivity analyses favoured pazopanib. Less fatigue and better overall QoL were the primary reasons for preferring pazopanib; less diarrhoea was the most cited reason for preferring sunitinib (see Figure 1). Physicians also preferred pazopanib over sunitinib (61% vs 22%; 17% expressed no preference). Pazopanib was superior to sunitinib in health-related QoL measures including fatigue, hand/foot soreness and mouth/throat soreness.

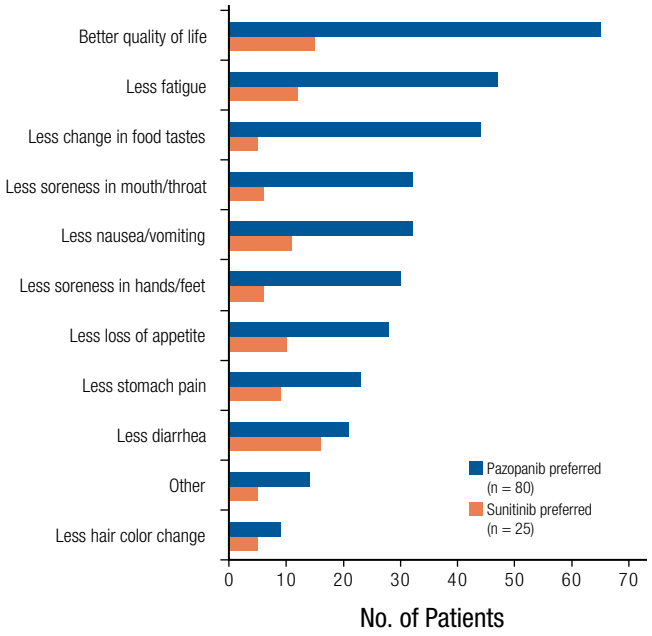

Figure 1: Common factors influencing patient preference. (Adapted from Escudier B et al. 2014[2])

Comment: In view of the previous studies showing noninferiority for pazopanib, a valuable consideration is the preference of patients for the two agents. This study had a double-blind, cross-over design to provide sophisticated information about the preference of patients. The reported data show a clear preference of patients (and doctors) for pazopanib. There was a period effect evident whereby patients generally preferred the first drug administered. This period effect is common in cross-over studies and was adjusted for. The preference score was a single rating performed at the end of the second drug administration. This corresponded to day 28 on sunitinib and this may have coloured the preference for sunitinib compared to a day 42 assessment when toxic effects have diminished.

The toxicity profiles were very similar to the Motzer study (above). The FACT-F fatigue scale showed a significant difference in favour of pazopanib and QoL scores relating to sore throat and hand-foot discomfort favored pazopanib. The dose intensities for both drugs were similar. Despite the preference for pazopanib there were more premature discontinuations because of adverse events with this agent. There were similar discontinuation rates for both drugs in period one, but in period two, 31% withdrew from pazopanib compared to 15% with sunitinib. Unfortunately the reasons for discontinuation were not provided.

Concluding remarks and take-home messages

The investigations discussed here highlight the activity of pazopanib and sunitinib against metastatic RCC. They represent valuable advances in therapy compared to the pre-molecular era. However, toxicities remain problematic as evidenced by 10-15% of patients withdrawing from treatment due to adverse events. Despite the similar withdrawal rate with both drugs there seems to be a clear patient preference for pazopanib.

The different toxicity profiles of pazopanib and sunitinib may reflect the slightly different molecular targeting of these agents. Pharmacokinetic differences are also likely to play a part. The 50 mg dosing for sunitinib is the maximum tolerated dose (MTD) whereas the MTD for pazopanib is up to 2000 mg, in contrast to the recommended daily dose of 800 mg. In addition, the half-life of sunitinib is 60 hours, which results in accumulating concentrations, which require a scheduled interval off treatment. Continuous administration of sunitinib at lower doses may be theoretically preferable but at present there is insufficient evidence to justify this approach and 50 mg daily remains the gold standard.

When treating advanced, incurable cancers the QoL of patients and associated patient preferences are vital considerations. Pazopanib is therefore a valuable alternative in the treatment of advanced and/or metastatic RCC. The investigators responsible for these studies should be congratulated for including rigorous QoL assessments to inform decision-making.

Product overview: Pazopanib in advanced renal cell carcinoma

- Pazopanib is an orally administered multi-TKI
- Pazopanib predominantly targets VEGFR-1, -2 and -3, PDGFR-α and -β, and c-Kit
- Pazopanib is non-inferior to sunitinib with regard to progression-free survival
- In clinical trials, patients prefer pazopanib over sunitinib with regard to tolerability/QoL
- The tolerability profile of pazopanib is distinct to that of sunitinib.

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