Renal cell carcinoma

**IS PAZOPANIB THE PREFERRED FIRST-LINE TREATMENT FOR METASTATIC RENAL CELL CARCINOMA?**

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**COMMENTARY:** Highlights of the 8th Annual Meeting of the Canadian Association of Genitourinary Medical Oncologists included a debate between Dr. Kylea Potvin from the London Health Sciences Centre and Dr. Piotr Czaykowski of CancerCare Manitoba in Winnipeg on the optimal treatment for metastatic renal cell carcinoma.

Sunitinib is an oral small molecule multikinase inhibitor considered the de facto standard of care in first-line treatment for patients with metastatic clear cell renal cell cancer. Pazopanib is another multikinase inhibitor active in renal cell cancer. Although both agents are believed to exert their clinical effects through inhibition of vascular endothelial growth factor receptors (VEGFR), pazopanib has been proposed as an equally efficacious but less-toxic alternative to sunitinib. At the time of the debate, results of a first-line open-label randomized trial comparing sunitinib with pazopanib using a noninferiority design had been presented at the 2012 European Society of Medical Oncology (ESMO) Annual Meeting. More recently, the results of the trial have been formally published.

The debaters provided a spirited and entertaining debate that identified the most important issues when reviewing these results and considering their application in clinical practice.

The motion proposed for debate was: “Pazopanib is the preferred first-line treatment for metastatic renal cell carcinoma.” Dr. Czaykowski argued the affirmative and Dr. Potvin the negative.

**SUMMARY:** Yes, pazopanib is the preferred first-line treatment for metastatic renal cell carcinoma

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Metastatic renal cell carcinoma (mRCC) can be an unpredictable disease, but in most patients it is relentlessly progressive and leads to substantial morbidity and, ultimately, death. With 6 new agents licensed in Canada for the management of advanced renal cell carcinoma (RCC), we are now in an era when we can select the most appropriate treatment based on published efficacy and toxicity data.

For patients with metastatic clear cell renal cell carcinoma (mCCRCC) who have good- or intermediate-prognosis disease based on Memorial Sloan-Kettering Cancer Center (MSKCC) or Heng criteria, the standard first-line therapy has been the oral agent sunitinib, which doubles the progression-free survival (PFS) duration compared to interferon-alpha. However, sunitinib therapy is often accompanied by bothersome toxicity, necessitating dose and schedule adjustments. Although a number of studies have postulated that the standard dose and schedule of sunitinib are not optimal and underplay this agent’s true benefit and tolerability, there are no data from randomized trials to support this contention. The highest quality evidence suggests that the standard approved dosing of sunitinib is often difficult to tolerate.

A well-designed randomized controlled trial (RCT) of first-line pazopanib vs sunitinib has now been published.

The COMPARZ trial included 1,110 patients with mCCRCC. The subjects had received no prior systemic therapy and had measurable disease with a good performance status and adequate organ function. Subjects were randomized to pazopanib 800 mg once daily vs sunitinib in standard dosing (50 mg daily for 4 weeks on, followed by 2 weeks off). The study was powered to demonstrate the noninferiority of pazopanib in regard to PFS.

The results of the COMPARZ study are clear. Pazopanib is noninferior to sunitinib, with a hazard ratio (HR) of 1.05 and a 95% confidence interval (CI) of 0.90 to 1.22. In numerical terms, this translates to a median PFS of 8.4 months for pazopanib vs 9.5 months with sunitinib. Visually inspecting the PFS Kaplan-Meier curves demonstrates that they are essentially superimposable. Median overall survival (OS) is 28.4 months with pazopanib and 29.3 months with sunitinib (HR actually favours pazopanib at 0.91, 95% CI 0.76–1.08; p=0.28), and pazopanib is also numerically superior in terms of independently verified partial and complete responses (31% vs 25%; p=0.03).

There were no significant differences in the need for treatment interruption, dose reduction or treatment discontinuation. More fatal adverse events (AEs) were reported for sunitinib (19 events) than for pazopanib (13 events). Pazopanib use was associated with a higher incidence of hepatic toxicity, namely rises in transaminases and bilirubin (17% grade 3–4 ALT elevation), but this led to discontinuation in only 6% of patients.

Of great interest is the fact that pazopanib is clearly better tolerated than sunitinib. The COMPARZ study did a commendable job of tracking health-related quality of life (HRQOL) using 4 validated tools. Assessments were performed at baseline, on day 28 of cycles 1 through 9 and on day 42 of subsequent cycles. Changes in mean scores over
time were analyzed for 11 of 14 HRQOL domains using standard statistical methodology. These analyses favoured pazopanib in each instance, with varying degrees of magnitude. In particular, subjects had significantly less fatigue and foot soreness with pazopanib. Even with evaluation at day 42 in each arm, the trends persisted.

To bolster these HRQOL data, a companion study, the PISCES study, was reported at the ASCO Annual Meeting in 2012. Subjects were randomly assigned to commence treatment with pazopanib or sunitinib in a double-blind fashion, with a crossover after 12 weeks. Patient and physician preference was ascertained. Both patients and physicians preferred pazopanib (70% and 61%, respectively), primarily because of reduced fatigue.

It is generally accepted that RCTs constitute the highest level of medical evidence. The available data from such trials confirm that pazopanib is equivalent to sunitinib in terms of clinical benefit (PFS, OS, response rates), is associated with a better HRQOL, and is preferred by patients who have experienced both agents in sequential fashion. Assuming equivalent cost of the 2 drugs, and reasonable vigilance for hepatotoxicity, it is readily apparent that pazopanib trumps sunitinib and should be considered the standard first-line therapy for mCCCRCC.

**SUMMARY:** No, pazopanib is not the preferred first-line treatment for metastatic renal cell carcinoma.

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When evidence demonstrates that 2 options are equally effective, the dilemma facing clinicians is, “How do I make the right choice?” The recent publication of the COMPARZ trial comparing pazopanib to sunitinib in previously untreated patients with mRCC highlights this predicament. The authors conclude that pazopanib should be favoured for safety and quality of life (QOL) reasons, but should we accept this conclusion at face value? A similar level of medical evidence. The available data from such trials confirm that pazopanib is equivalent to sunitinib in terms of clinical benefit (PFS, OS, response rates), is associated with a better HRQOL, and is preferred by patients who have experienced both agents in sequential fashion. Assuming equivalent cost of the 2 drugs, and reasonable vigilance for hepatotoxicity, it is readily apparent that pazopanib trumps sunitinib and should be considered the standard first-line therapy for mCCCRCC.

PISCES study, a blinded and randomized sequencing of sunitinib followed by pazopanib or vice versa for a 22-week period, with QOL assessments every 2 weeks. While the authors conclude that patients preferred pazopanib, they do not address the magnitude of preference. Furthermore, they do not consider efficacy, which could significantly weigh upon a patient’s choice of treatment, irrespective of toxicity. While 11 of 15 QOL parameters in COMPARZ were statistically significant, only the difference in mouth and throat soreness was of a medium-to-large effect size. The effect sizes in the remaining parameters were either small-to-medium or negligible. Statistical significance does not always equate with clinical significance.

Clinical trials are necessarily restrictive to show robust outcomes. However, this makes application of the results a challenge in the real world. A decade of clinical experience with sunitinib has provided insights into the drug’s flexibility of use. Progression of disease has been noted with even brief breaks in sunitinib therapy, which is relevant as there is a significant association between sunitinib exposure and improved clinical outcomes in mRCC. Several retrospective studies and one prospective study have been reported using alternative dosing schedules of sunitinib; while toxicity has been substantially lower, there has been no obvious loss of efficacy. A recently published retrospective study of 185 patients with mRCC compared traditional scheduling (TS) to alternate scheduling (AS) of sunitinib to determine the impact of AS on clinical outcomes. Throughout the study, 53% of patients remained on TS dosing, while 47% initiated or transitioned to AS. Median OS was 17.7 months on TS (95% CI, 10.8–22.2), as compared with 33 months (95% CI, 29.3–not estimable) on AS (p=0.0001), with a significantly longer time on treatment (TOT) for the AS group (4.1 months vs. 13.6 months; p=0.0001). The incidence of AEs decreased significantly for patients started on or transitioned to AS.

Finally, the purpose of a noninferiority study is to prove that a new treatment is not worse than the standard therapy. Therefore, analyzing subjects according to the treatment actually received (per-protocol) is the outcome of most value, and often of greatest interest to regulatory bodies. In this study, it is worth emphasizing that the per-protocol analysis does not quite meet the predefined criteria (<1.25 HR for progression of disease or death, 1.07; 95% CI 0.91–1.25).
In their publication on practising and teaching evidence-based medicine (EBM), Straus and colleagues note that EBM requires the integration of the best research evidence with our clinical expertise and our patient’s unique values and circumstances. This tenet embodies the art of medicine — in essence, how we make the right choice. Although COMPARZ met a statistical endpoint, the conclusions ignore our experience and ability to optimize and individualize treatment with sunitinib. While pazopanib is a choice, sunitinib remains the choice.

References


