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EDITORIAL

Cost-effectiveness of pazopanib: an example of improved transparency and accessibility of industry-sponsored economic evaluations through publication in peer-reviewed journals

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We congratulate Amdahl *et al.*[1] on publishing their paper about the cost-effectiveness of pazopanib compared with sunitinib in metastatic renal cell carcinoma (mRCC) in Canada. The article reports an analysis similar to the one submitted to the pan-Canadian Oncology Drug Review to support the funding request for pazopanib in mRCC, updated with final overall survival (OS) data from the pivotal trial[2]. Economic evaluations in oncology are increasingly important to guide both policy and practice. We commend the efforts of these authors to put their submitted analyses into the public domain for transparency and to support and inform future research.

The base-case analysis (using the list prices of pazopanib and sunitinib) by Amdahl *et al.*[1] found that, compared with sunitinib, which is the standard of care for first-line therapy in mRCC, first-line pazopanib is likely cost-saving. The base case analysis also suggested that pazopanib might be slightly more effective than sunitinib numerically, with an incremental gain of 0.057 life-years and 0.059 quality-adjusted life-years. Before concluding that pazopanib is dominant (that is, it provides more benefit for a lower cost) with respect to sunitinib, it is important to review the clinical data comparing pazopanib and sunitinib in mRCC to assess the comparative efficacy and preference-based measures of health-related quality of life (HRQOL) associated with those agents—that is, their health utilities—to examine the face validity of the economic model in its base case.

The efficacy differences between the pazopanib and sunitinib in the COMPARZ study[3] were not statistically significant, median progression-free survival for pazopanib and sunitinib being 8.4 months [95% confidence interval (CI): 8.3 to 10.9 months] and 9.5 months (95% CI: 8.3 to 11.1 months) respectively, with a hazard ratio of 1.05 (95% CI: 0.90 to 1.22). The study met its primary endpoint of non-inferiority in progression-free survival. No OS difference was observed in the COMPARZ study, in which median OS was 28.4 months for pazopanib (95% CI: 26.2 to 35.6 months) and 29.3 months for sunitinib (95% CI: 25.3 to 32.5 months), with a hazard ratio of 0.91 (95% CI: 0.76 to 1.08). At the updated analysis, OS was similar in the two groups (hazard ratio for pazopanib vs. sunitinib: 0.92; 95% CI: 0.79 to 1.06; $p = 0.24$)[2].

With similar survival results for pazopanib and sunitinib based on the COMPARZ study, one might ask, "How did the model project an incremental gain of 0.057 life-years in favour of pazopanib?" The model actually projected a shorter life expectancy while patients were taking pazopanib than while their counterparts were taking sunitinib (0.013 life-years lost in the progression-free state). However, the model also projected that, after patients progressed and stopped taking pazopanib, their life expectancy was longer than it was for patients who received sunitinib (0.070 life-years gained in the post-progression state). Together, the loss and the gain resulted in a net gain in life expectancy for pazopanib, implying that the survival benefit of pazopanib acted only after progression, when patients were no longer taking pazopanib. There is no biologic basis for that phenomenon, and it likely simply reflects small numerical differences between the pazopanib and sunitinib progression-free survival and OS curves, without accounting for uncertainty. Interestingly, the model also predicted that pazopanib would be more effective in at least 80% (or possibly all) of the simulations despite the nonsignificant result.

Although the COMPARZ study[3] collected some HRQOL measures, it did not collect preference-based measures of HRQOL to allow for the calculation of quality-adjusted life-years for the purpose of economic evaluation. The PISCES study[4]—a randomized, double-blind trial with a crossover design (that is, pazopanib→sunitinib vs. sunitinib→pazopanib)—had, as its primary endpoint, an examination of patient preference for either pazopanib or sunitinib, which suggested that patients preferred pazopanib over sunitinib. However, the study had a few limitations[5], including a relatively high proportion of the randomly assigned patients (33%) not being evaluable for the primary endpoint, and the analysis of the pazopanib preference being based on a "modified" intention-to-treat population. The EQ-5D (EuroQoL Group, Rotterdam, Netherlands) was also collected as the preference-based measure of HRQOL in the PISCES study[4], but the EQ-5D results would have been subject to similar limitations. The data from the PISCES study were used in the submission to the pan-Canadian Oncology Drug Review.

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In the updated analysis[1], the authors conducted a regression based on patients in a trial comparing pazopanib with placebo[6], assuming that the effect of adverse events (AEs) were driving the differences in HRQOL, regardless of actual treatment received. For the analysis, the AEs were grouped by severity and whether the AEs were more commonly occurring in the sunitinib or the pazopanib group of the COMPARZ trial. Using that approach, the regression model found that the health utility decrement was larger for the group of AEs more commonly occurring in patients who used sunitinib than for the remaining AEs more frequently occurring in patients who used pazopanib in the COMPARZ trial. The results of the regression model were combined with the incidence and duration of AEs in each treatment arm to derive the mean utility values used in the model, producing mean utility values of 0.7089 (standard error: 0.0193) for pazopanib and 0.6832 (standard error: 0.0236) for sunitinib, an incremental difference of 0.0257 in the progression-free period[1]. Given that the COMPARZ trial demonstrated similar efficacy and a more favourable toxicity profile for pazopanib, it is not unreasonable that the point estimate of the utility score could slightly favour the pazopanib group. However, these mean utility values were not directly derived and might be neither statistically nor clinically different, especially because the difference was smaller than the reported estimates of minimal important differences for health utilities (which are in the range of 0.05–0.08 for the EQ-5D)[7,8]. Thus, it is somewhat difficult to conclude from those data that pazopanib is associated with better utility than sunitinib. It might be reasonable to conservatively expect that the utilities of pazopanib and sunitinib are fairly similar given the size of the standard errors of the two utilities, subject to a reasonable amount of uncertainty[9,10].

Given that clinical trials did not demonstrate a statistically significant survival benefit or EQ-5D health utility benefit for pazopanib over sunitinib, we feel that an appropriate interpretation could be that the study findings suggest similar efficacy and health utility for the two drugs. Reasonably, the pan-Canadian Oncology Drug Review's Expert Review Committee also concluded that it is reasonable to assume similar efficacy and to focus on the cost comparison between pazopanib and sunitinib in this setting[11].

We appreciate that the sensitivity analyses by Amdahl *et al.*[1] address all the considerations discussed here, including the importance of the relative price of the two drugs. The authors demonstrate as part of their additional analyses that—assuming similar efficacy, health utility, and daily price of the two therapies—only minor cost differences remain. Thus, interpreting the analyses in light of the evidence, it appears that these two options for first-line therapy in MRCC might be largely similar and, taking into account the relative prices of the two drugs, the hope would be that, after confidential negotiations, they will also be similar in cost. In that case, having both drugs available would give patients the option to choose based on individual preference and side effect profile, especially in the case of intolerance to one of the drugs, and would ensure that health care resources are being efficiently used.

The generalizability of the study findings remains to be seen in practice. Verification from experience is needed to know whether the comparative outcomes as laid out will be realized. In Canada, jurisdictions have an important opportunity and challenge to evaluate the real-world effectiveness and cost-effectiveness of therapies in clinical practice after drugs are funded. Moreover, post-market research can provide valuable insights into practice patterns when two alternatives are funded and can possibly inform continued uncertainties such as sequencing and long-term adverse effects.

We applaud the approach of the authors to share their analyses with the broader clinical and research communities, and we encourage more authors of economic evaluations created and submitted to review bodies (for example, the Canadian Agency for Drugs and Technologies in Health, the pan-Canadian Oncology Drug Review) to follow suit. We expect that this activity will build on the principle of transparency being increasingly championed by the review organizations and will improve the rigour of the economic evidence used to inform policy. Finally, we call on the community to continue to pursue both academic merit and clinical and policy relevance by supporting the availability of peer-reviewed publications of economic evaluations to inform the reimbursement review process. Ideally, it would be helpful if economic evaluations were to be published before decision-making so as to engage more stakeholders in the discussion[12]. In doing so, the clinical and economic evidence bases supporting the health technology assessment processes in Canada might be brought into better alignment, improving the robustness of decision-making and ultimately helping health care systems in Canada to provide effective and appropriate care to patients.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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