Health Care Costs Among Renal Cancer Patients Using Pazopanib and Sunitinib

Publications that aim to assess the economics of different therapies are important because they complement clinical trial data and may aid in decision making. We therefore read with interest the study by Hansen et al. in the January 2015 issue of JMCP. This study compared costs between pazopanib (PAZ) and sunitinib (SU) in the first-line treatment of patients with metastatic renal cell carcinoma (mRCC).1

The authors assessed health care costs through assignment of costs from the Truven Health MarketScan Databases to the self-reported health care resource utilization (HCRU) data from the population studied in the phase III noninferiority clinical trial COMPARZ (Pazopanib versus sunitinib in metastatic renal cell carcinoma).2 We are writing to comment on the conclusions drawn from the results presented, the methodology used, and to request additional information and clarification on data presented.

Most importantly, Hansen et al.’s conclusion that health care costs were consistently lower among PAZ versus SU patients is not supported by the results reported. The main results as presented in Table 2, Figure 2, and Table 3 in the Hansen et al. study report no significant difference between SU and PAZ. Appendix C shows that only 2 of the 30 HCRU rates from the COMPARZ trial (emergency department visits and radiological visits) were significantly different. Multiplying these 2 HCRU items with their corresponding unit costs—unit costs of radiological visits were not reported, but in the same journal issue, Delea et al. report use of $75.77—results in an economically nonmeaningful cost advantage for PAZ of $48 over a 10-month period.

An earlier version of the Hansen et al. article was available online (approximately between December 22, 2014-February 26, 2015) but was withdrawn from the website (between February 27, 2015-April 6, 2015) presumably to correct for use of incorrect drug costs for PAZ and SU. Reanalyses, incorporating revised drug costs, were undertaken yielding considerably different results compared with the initial article. In the revised analyses, almost all results are nonsignificant, whereas previously most of the results were significant. However, despite these important changes in results, the authors’ wording and conclusions remain almost identical to the original article. The reader is left with the impression that there are important cost differences between the drugs despite the fact that the reanalyses contradict the original findings.

There are several methodological issues in the Hansen et al. study. The value of the adjusted analyses using regional variables reported in Table 3 and Appendices D-F is in question, since the authors do not report if regional- or country-level cost data were used. If the analyses used U.S. costs only, the regional estimates are not applicable and cannot be interpreted. The same is true for the model estimates of the cost difference between PAZ and SU. Apart from this issue, the adjusted analyses for the United States shows only that 1 of 3 models, the ordinary least squares (OLS), was significant (Appendices D-F). However, an OLS model is usually not appropriate for cost estimation because costs are often non-normally distributed and generally skewed to the right, with a small fraction of patients accounting for the majority of the cost. The authors acknowledge that costs remain skewed even after excluding the 1% of patients that were outliers, and the inappropriateness of the OLS method is evident, since the drug cost estimates (Appendix D) were much lower compared with all other analyses.

Comparing the different versions of the article further indicates problems with the adjusted analyses. For instance, in Table 3 the estimated cost difference is lower for PAZ and SU in the revised version despite the fact that the study drug cost difference is much higher (Table 2B). Adding adverse events (AEs) resulted in an increased cost difference of $6,225 in the revised version, compared with $1,153 in the initial version, despite the fact that AE costs should not have changed. The regional estimates have changed signs in the revised version, with costs in all other regions being numerically higher compared with North America, and the revised results suggest that European costs are also statistically significantly higher ($14,748)—an anomalous finding. Similar inconsistencies are evident in Appendices D-F. Furthermore, there is no information on the process of variable selection and determination of the final model for the adjusted analyses or summary statistics describing model performance, which would help the reader understand the models’ predictability and the strength of the results. Hence, the models applied and the results in Table 3 and Appendices D-F, while generally showing no cost differences between SU and PAZ, are hard to understand or validate.

Only the Kaplan-Meier sample average (KMSA) results seem to demonstrate a cost difference that was statistically significant. However, there is limited information on how the KMSA estimation technique was applied. For instance, how were drug costs calculated? What was the source for the survival data? Were covariates used as indicated by reference to Lin, et al.?7 The total costs for PAZ and SU ($143,585 and $156,128, respectively) seem overestimated when compared with the other results in the study, as well as in the companion article by Delea et al. ($77,356 and $86,854, respectively), which similarly used survival analysis to model drug and HCRU costs over the entire course of treatment.5,4 We therefore request further information as to how the authors arrived at the results for the KMSA analysis.

Two other issues are worth noting. First, the authors state use of wholesale acquisition cost (WAC) for calculations of drug costs. Rather than use the same reference date, the authors chose different time points for each drug—for PAZ the month prior to a price increase (January 2013) and for SU the month when a price increase occurred (July 2013).5 Moreover, the authors do not cite a reference nor do they state the actual monthly drug costs, duration of treatment or adjustments for
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dosing schedules, or dose intensity. We request clarification on how the drug costs were calculated and the sources for the inputs into the calculations. A description of actual costs observed in the Truven Health MarketScan Databases would have served to validate the WAC drug costs used.

Second, Hansen et al. also attempt to quantify costs of AEs reported in COMPARZ through inclusion of grades 3/4 AEs occurring at ≥2% incidence and “most likely to influence resource use and cost and that could also be identified by ICD-9-CM diagnosis codes from the MarketScan databases.” Identification of AEs in claims data is unreliable, and discerning severity such as grade 3 and 4 is not possible. Nevertheless, the wording of the conclusion gives the impression that results were driven by grade 3 and 4 AEs. Furthermore, we question the addition of AE costs as a separate category, since realistically, any differences in AE costs should be reflected in total HCRU costs. This is also the assumption by Delea et al.3

Finally, we agree with the authors’ stated limitations of the study, including their concerns about representativeness with respect to costs being highly localized and results not reflecting the real-world setting.

In summary, the study by Hansen et al. fails to show any cost differences between SU and PAZ in the treatment of mRCC that are consistent or significant. The conclusion should therefore be revised accordingly.

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DISCLOSURES
The authors are employed by Pfizer.

REFERENCES
The Authors Respond

We appreciate the thoughtful comments by MacLean et al. on our study. We would first like to clarify that we did identify an error in analyzing the study drug utilization doses from the clinical trial database. This resulted in extremely low drug costs for pazopanib and sunitinib, and in consultation with the JMCP editor-in-chief, we revised the analyses and the article to correct that error. Making comparisons between the versions is irrelevant in our view. Here, we address the address and the concerns raised by MacLean et al. using the published version of the study.

Our main conclusion is that the observed differences in total cost between pazopanib- and sunitinib-treated patients were consistently similar, not that they were statistically significant. Total costs for pazopanib recipients were between $1,900 (unadjusted) and $12,500 (the Kaplan-Meier sample average [KMSA]) lower than sunitinib patients, depending on the method considered. We believe these are meaningful differences for patients with advanced renal cell carcinoma and the payers that reimburse the costs of health care.

We acknowledge that cost data are not normally distributed and, as a consequence, used different approaches to better understand the association between costs and treatment. Rather than reporting the “best” result for pazopanib, we chose to show all of the results.

The resource use data were regionally collected, and U.S. unit costs were applied. We believe that the regression coefficients representing the country-level covariates are interpretable in relative terms, even though the estimates themselves do not represent precise country-specific differences.

For the KMSA analysis, we divided the observation periods into monthly intervals over the trial’s 40-month follow-up period. Costs and survival for each individual per month were used to estimate the monthly weighted costs, which were then summed across the follow-up period. The KMSA estimate produces higher estimates than traditional regression methods because it more highly weights earlier periods in the study, where costs are highest. KMSA is the most accurate estimator because it is robust to skewed data and accounts for censoring in time-to-event studies.

The wholesale acquisition costs (WAC) used in our study were the most currently available for each drug at the time we performed our analysis. The different dates were simply when the most recent price updates occurred; however, the prices were current at the time our analyses were carried out (August 2013). The WAC price used for pazopanib (as of January 2013) was $59.42 per 200 mg tablet. The WAC prices used for sunitinib (as of July 2013) were $109.41 for the 12.5 mg capsules, $218.82 for the 25 mg capsules, and $403.56 for the 50 mg capsules. Claims from the MarketScan databases from the period that were available at the time of our study would not have provided valid prices for either drug.

We did not identify adverse events in MarketScan; rather, we used adverse event rates reported in the COMPARZ trial. We compared the costs of patients with documented grade 3 or 4 adverse events to those who did not.

Thank you again for your comments and the opportunity to clarify our study.

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