



Letter to the Editor

Safety of multikinase inhibitors in metastatic renal cell carcinoma and indirect treatment comparisons

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To the Editor

I have read with great interest the article by Powles and colleagues¹ on an indirect comparison of the toxicity of sunitinib and pazopanib in patients with metastatic renal cell carcinoma (mRCC). Indeed, methods such as indirect treatment comparisons and, more recently, multiple-treatment comparisons using network meta-analysis, have been proposed when head-to-head evidence is not available or is not sufficient to guide medical decision-making. Powles and colleagues concluded that “[the analysis] suggests sunitinib and pazopanib have distinct toxicity profiles which may help guide patient’s choice.” However, there are some points to be concerned. First, in their indirect comparison,¹ the authors applied a simple but inappropriate method to compare the results of individual arms from different uncontrolled trials as if they were from the same trial. This type of naïve indirect comparison has been extensively criticised for discarding the within trial comparison, increasing liability to bias and over-precise estimates.^{2–4} Second, certainly limited by the nature of the two open label single arm pilot trials (with less than 50 patients each), the authors just reported safety data for a selection of common toxicities.

In my opinion, an alternative approach can take advantage of the strength of randomised evidence in making unbiased hypothesis-generating comparisons.

For example, an exploratory calculation of an indirect effect size can be done for the class of multikinase inhibitors (e.g. sunitinib, pazopanib and sorafenib) by comparing the results of their direct comparisons with a common control group (e.g. placebo and/or interferon- α) considering available data from phase II–III randomised controlled trials and assuming the “transitive property” (if A is much better than B, and B is better than C then A is assumed to be better than C). To illustrate this point in part, I concentrate on the important risk of hypertension not assessed in the indirect comparison by Powles and colleagues. Reports from a recent systematic review of the efficacy of these therapies⁵ allow the presentation of a simple network of four controlled trials^{6–9} including 1214 mRCC patients randomly allocated to sunitinib, pazopanib or sorafenib (Fig. 1).

In the direct comparison of sorafenib versus placebo (17% versus 1%),⁶ the relative risk (RR) for hypertension was 15.6 (95% confidence interval [CI], 6.4–38.1) and 4.2 (95% CI, 1.6–10.6) for sorafenib versus INF- α (23% versus 5%).⁷ The values of RR for the other direct comparisons were 7.5 (95% CI, 4.3–13.0) for sunitinib versus INF- α (30% versus 4%)⁸ and 3.8 (95% CI, 2.3–6.3) for pazopanib versus placebo (40% versus 10%).⁹

In the indirect comparison of sorafenib versus pazopanib, the RR for the end-point was 4.1 (95% CI, 1.6–10.1) and 0.6 (95% CI, 0.2–1.6) for sorafenib versus sunitinib. The RR for a third (exploratory) indirect comparison of pazopanib versus sunitinib was 0.14 (95% CI, 0.03–0.6). Interestingly, these exploratory results suggest

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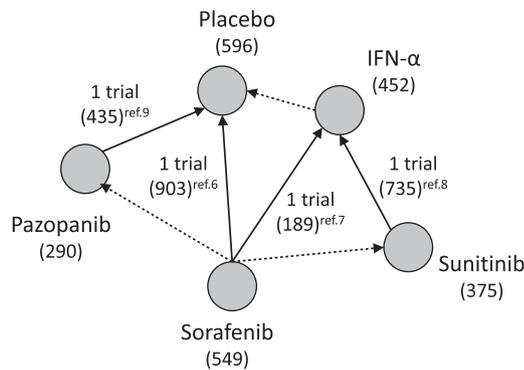


Fig. 1. Evidence network of direct and indirect comparisons for safety outcomes. Number of randomised patients is shown in parentheses. Solid lines represent direct comparisons within randomised controlled trials. Dotted lines represent indirect comparisons within randomised controlled trials.

differences in safety profile for these competitive alternatives, but the latter should be confirmed by ‘methodologically sound’ double-blind, active-comparator randomised controlled trials.

It is important to note, however, that even though this evidence synthesis approach includes a large number of patients from several single trials, the evidence network should be completed with continuing trials (e.g. Patient Preference Study of Pazopanib Versus Sunitinib in Advanced or Metastatic Cancer - ClinicalTrials.gov identifier: NCT01064310 (PISCES) and Pazopanib versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma - ClinicalTrials.gov identifier: NCT00720941 (COMPARZ) trials) and unpublished trials examining the wide clinical research programme.¹⁰ Certainly, indirect comparisons based on single trials need to be interpreted cautiously in the clinical setting. Moreover, potential biases in a field-at-large influenced by commercial third parties (publication bias) could lead to invalid results.

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Conflict of interest statement

I have declared that no competing interest exists. The views expressed are those of the author and should not be understood or quoted as being made on behalf or reflecting the position of any academic or public health institution.

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