Reviewer's report

Title: Metastatic renal cell cancer treatments: A mixed treatment comparison meta-analysis involving more than 4,800 patients

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Reviewer: Chris Coppin

Reviewer's report:

Strengths:

This is a timely analysis of a hot topic, randomized trials of targeted drugs for renal cell cancer. The authors conduct a duplicate systematic search of multiple databases up to early April 2008, evaluate study eligibility and quality using clearly stated criteria, endeavour to supplement data gaps by contacting study investigators, and tabulate eight eligible studies in detail. This is more up to date then the systematic review of the same topic published in the latest update of the Cochrane Library. Progression-free survival is chosen as the main endpoint of their analysis, a pragmatic and reasonable decision given that most studies are insufficiently mature to address overall survival. The authors use an interesting analytic method that will be unfamiliar to most oncologists, including this reviewer, that attempts to establish a hierarchy of efficacy of the agents based on indirect as well as directly tested comparisons.

Weaknesses:

Major Compulsory Revisions

1. Studies used for indirect/mixed comparison must be restricted to reasonably comparable patient groups to avoid giving some agents an unfair advantage if tested only in favourable situations (eg sunitinib for first-line clear cell). First and second-line therapy for advanced renal cancer are clearly different clinical situations, with different pre-targeted era standard therapy and key outcomes (interferon-alfa/survival benefit, and placebo/palliation, respectively). These issues could be reasonably addressed by (a) separate analysis of first-line and second-line trials, and (b) casting the results of mixed meta-analysis as hypothesis generating. The unqualified used of HRs with 95% CIs gives the uninformed reader a misleading sense of accuracy. If these points are a reflection of reviewer misunderstanding of the strength of the statistical methods used, they must be very specifically addressed and the methods rigorously assessed by a statistician familiar with the issues.

2. The authors appear to equate progression-free survival (PFS) with ‘survival’ and this is quite unacceptable (readers will take ‘survival’ to mean overall survival). PFS is biologically interesting but is not a surrogate predictor for overall survival and is not a clinical endpoint (clinical endpoints are quality and quantity of life). Overall survival has not yet shown significant improvement apart from a
small effect with temsirolimus. The following statements must be removed or revised: “new interventions…provide a high level of protection for mRCC..” [abstract conclusion]; “sunitinib….have shown positive survival endpoints…in phase III trials” [introduction]; “our study demonstrates consistent survival benefits with the new targeted…” [discussion, third sentence]; “the current…agents…extend life and reduce mortality” [penultimate sentence].

Minor Essential Revisions

3. The report is full of writing errors such as “immediate” for “intermediate” prognosis (repeatedly in text and in table 1), “imitations” for “limitations” (discussion para 2), etc. It is hard to believe that any of the five authors have read this report carefully.

4. The abstract results are unintelligible.

5. The search strategy refers to an information specialist (PR) that does not correspond to any listed author.

6. The figures require legends eg fig 2 does not state the outcome evaluated, fig 3 should be the centerpiece with explanation, and fig 4 refers to “RR”.

7. A conflict of interest statement is essential given that some of the conclusions will be seized upon by the ‘winning’ pharmaceutical companies and weaknesses scrutinized by the ‘losers’.

8. Table 2 intervention & control columns have errors: eg Bukowski 2007 tested BEV+erlotinib, Rini and Escudier studies tested BEV+IFN, and Escudier was placebo-controlled.

9. References need to be checked. Ref #36 is 2003, not 2007. ASCO abstracts need to be clarified eg ref #32 is Proc ASCO abstr#5033, not just JCO 25:5033.

Declaration of competing interests:

I have no conflict of interest except that I am a Cochrane Collaboration reviewer for the same topic. I agree to have my comments published in the event the article is accepted.