Author’s response to reviews

Title: Systematic Review of topotecan (Hycamtin) in relapsed small cell lung cancer

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Author’s response to reviews: see over
Dear Editor,

We have uploaded our revised manuscript. Our responses to referees’ comments can be found below.

We have not added an acknowledgement section as suggested, because apart from the authors, no-one was involved in the preparation of this manuscript.

Sources of funding for the study, for each author, and for the manuscript preparation are described in the ‘competing interests’ section.

All changes to the manuscript have been highlighted using track changes.

Best wishes,
Rob Riemsma

Referee 1 - Lucio Crinò

This is a well written systematic review on topotecan as second line treatment in SCLC after failure of first line treatment. Second line therapy in SCLC, is a poorly studied and difficult topic, with few randomised studies and small data on comparator arms such as best supportive care. This review has been designed with a clear and rigorous methodology selecting just seven trials in which however, heterogeneity in patient’s selection and drugs doses make the conclusions poorly comparable. Despite these considerations and the objective lack of experience, the research has been performed with a careful design and all the conclusive statements seem to be at the same time equilibrate and consistent with the actual clinical evidence. In summary, I think that this review can be very useful from a clinical point of view, and it deserves publication on BMC Cancer.

Thank you!
No response required.

Referee 2 - Paul Lorigan

This is an interesting analysis and interpretation of the data on this topic. The data individual trials have already been subjected to peer review and are generally well accepted. Indeed, NICE has accepted that oral topotecan is essentially equivalent to intravenous (iv), and has approved it for the second line treatment of patients with relapsed SCLC not suitable for anthracycline based chemotherapy. The authors have set out to see if indirect comparisons can be drawn between the trials. From the perspective of a clinician working in this area, I’m not convinced that this analysis of four trials adds anything to the interpretation of the individual studies.

Furthermore, I think that some of the conclusions are unjustified. I have set out my comments below

No response required.

Major compulsory revisions
1 The inclusion criteria for the two studies by von Pawel and the study by Eckhardt did not include that patients were unsuitable for retreatment with the first line regimen. So there studies do not fit with the inclusion criteria for the analysis. Only the study by O’Brien had this as an inclusion criteria.

The licence indication for topotecan states that it is for patients “for whom re-treatment with the first line regimen is not considered appropriate”. Patients in the three trials (Von Pawel 1999 & 2001 and Eckardt 2007) had recurrence at least 60 days, 3 months and 90 days after the end of first-line chemotherapy, respectively. For these patients re-treatment with first line therapy is the
2 By selecting full papers only, the authors have not included a randomized phase II study by Jotte et al, presented at the World Lung Cancer Congress 2009, of topotecan versus amrubicin in relapsed SCLC. This reported a response rate of 44% for amrubicin versus 11.5% for topotecan, with median overall survival of 9.3 versus 7.7 months in favour of amrubicin. The authors should also mention in the discussion that a large randomised Phase III study of topotecan versus amrubicin as second line therapy completed accrual in 2010 and is likely to report within the next 6-12 months. This needs to be addressed in the discussion as suggested.

3 The study by Inoue et al used a lower dose of topotecan, but the response rates for amrubicin are significantly higher than those ever published for topotecan, and in accordance with the study by Jotte et al, and by Ettinger et al (ASCO 2009). To date, there is no clear association between increased response rate and better survival in SCLC, but this may change. Furthermore, increased response rate is likely to result in better control of certain tumor related symptoms. These issues need to be addressed in the discussion.

4 Figure 4 is not referenced in the text. The columns are the opposite way round to figure 3 and the HR and CI slightly different. This needs to be explained. The lozenge for 1.1.1 appears to sit on the other side of unity than in Figure 3.

5 The statement that oral topotecan is at least as good as iv in terms of symptom control is purely speculative and shouldn’t be included in the conclusion. Only the von Pawel study looked at this. The numbers were small, but for many of the parameters (e.g. haemoptysis, shortness of breath) there was a trend towards a better outcome for iv.

Von Pawel 2001 and Eckardt 2007 reported symptom control for oral vs IV; none of the outcomes showed a significant difference. Therefore, we think the conclusion is justified.

6 The comment that oral topotecan is as good as CAV in terms of toxicity is also incorrect, given the there was more anaemia.

The difference for anaemia is not statistically significant.

Minor discretionary revisions
1 Page 11, end para 1. What does the phrase 'and accounted for prognostic factors it was 0.90 (95% CI, 0.55 to 1.47).’ mean?

Analyses were controlled for demographic and baseline characteristics such as: response and duration of response to previous therapy, sex, presence of renal impairment at baseline, performance status, presence of baseline liver metastases, extent of disease, previous radiotherapy, and maximum tumor diameter. This
2 Neutropenia appears to be less of a problem for oral than IV. However the incidence of neutropenic sepsis was the same in the Eckhart study (5% both arms) and not significantly different in the Von Pawel study (5.1% oral vs 3.3% iv). So this difference in neutropenia is no a major clinical benefit.

We agree that it appears as if there are no differences in clinical benefit, but due to the fact that the number of patients with sepsis is very small in both studies (2-3 patients in each arm of the von Pawel study and 7-8 patients in each arm of the Eckardt study) in our view power of both studies is too low to make any reliable assumptions on this issue.

Referee 3 - Yee C Ung

The authors present a thorough review and analysis on a narrow subject. One always has concerns about bias when the sponsor of the manuscript is also the producer of the drug in question. None the less, the authors have made a statement regarding any potential conflict of interest. The evidence for the use of topotecan is limited but the best evidence for its use is in the OBrien study evaluating oral topotecan and BSC vs BSC alone with a survival benefit in favor of topotecan. The other major premise is the ability to do an indirect comparison when no direct comparison trial is available providing the trials comprise comparable patient characteristics. The authors have provided some justification and comparisons to validate their argument. Ideally a direct comparisons trial would be better but for this patient population, its unlikely to happen. The conclusions given the limitations of the available data are appropriate.

Thank you! No response required.