Reviewer's report

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

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Reviewer: Paul Lorigan

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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

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 these studies do not fit with the inclusion criteria for the analysis. Only the study by O'Brien had this as an inclusion criteria.

2. By selecting full papers only, the authors have not included a randomised 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.

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 tumour related symptoms. These issues need to be addressed by the authors.

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.

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

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?

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.