# The clinical effectiveness and cost-effectiveness of topotecan for small cell lung cancer: a systematic review and economic evaluation

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## *Executive summary*

*Health Technology Assessment* 2010; Vol. 14: No. 19
DOI: 10.3310/hta14190

**Health Technology Assessment**
**NIHR HTA programme**
**www.hta.ac.uk**

# Executive summary

## Objectives

The aim of this systematic review and economic evaluation was to assess the clinical effectiveness and cost-effectiveness of topotecan as second-line treatment for small cell lung cancer (SCLC).

## Epidemiology and background

Lung cancer is one of the most common cancers, with SCLC accounting for approximately 10–20% of all lung cancers. Without treatment, SCLC has an aggressive clinical course, with life expectancy of between 6 weeks and 3.5 months. However, SCLC is initially very sensitive to chemotherapy and this is reflected in prolonged median survival rates. Second-line chemotherapy is offered to patients at relapse, and depends on the response and duration of response to first-line therapy, but generally consists of a repeat of the first-line chemotherapy regimen. However, for some relapsed patients, this may not be considered appropriate due to the development of resistance, contraindications or adverse events. In these patients, alternative chemotherapy regimens can be used. This assessment considers topotecan, used within its licensed indication as second-line treatment for patients with relapsed SCLC, compared to other chemotherapy regimens or best supportive care (BSC) on measures of disease progression and survival.

## Methods

### Data sources

A sensitive search strategy was designed and applied to 11 electronic bibliographic databases (including MEDLINE, EMBASE and the Cochrane library) from 1990 to February 2009. Bibliographies of related papers were screened, key cancer resources and symposia were searched, and experts were contacted to identify additional published and unpublished references. Manufacturer submissions to the National Institute for Health and Clinical Excellence (NICE) were also searched.

### Study selection

Titles and abstracts were screened for eligibility by two independent reviewers. Inclusion criteria were defined a priori and applied to the full text of retrieved papers by two reviewers using a standard form. Studies were included if the participants were adults (≥ 18 years) with relapsed SCLC who responded to first-line treatment and for whom re-treatment with first-line therapy was not considered appropriate; the treatment was topotecan [oral or intravenous (i.v.)] compared to one another, BSC or other chemotherapy regimens; the outcomes included measures of response or disease progression and measures of survival; the studies were randomised controlled trials.

### Data extraction and quality assessment

Data extraction and assessment of methodological quality was undertaken by one reviewer and checked by a second. Differences in opinion were resolved through discussion or recourse to a third reviewer at each stage. Authors of all the trials were contacted to clarify if participants met the licensed indication of topotecan.

### Data synthesis

The trials were reviewed in a narrative synthesis with full tabulation of the results of all included studies. Meta-analysis was not undertaken due to clinical heterogeneity in the patient groups and comparator treatments.

### Economic model

An independent economic model was developed to estimate the cost-effectiveness of topotecan (oral or i.v.) compared with BSC for patients with relapsed SCLC, for whom re-treatment with the first-line regimen was not considered appropriate, from the perspective of the National Health Service (NHS) and Personal Social Services (PSS). The model used survival analysis methods to derive estimates of mean survival for patients treated with topotecan or receiving BSC alone, which were combined with quality of life (QoL) weights to derive estimates of mean quality-adjusted life expectancy for patients receiving BSC alone or topotecan plus BSC. The

model includes an estimate of time to disease progression (TTP) for patients receiving topotecan, to take account of the reduction in QoL following disease progression.

Categories of costs included in the model include drug use, chemotherapy administration and on-treatment monitoring, management of adverse events, monitoring for disease progression and palliative care. Resource use in the model was estimated from included RCTs, other published sources and advice from clinical experts. Drug costs were unit costs taken for the *British National Formulary* (*BNF*). Other unit costs were taken from published sources (including NHS Reference Costs) and from Southampton University Hospitals Trust.

The base-case model has a 5-year time horizon. Costs and health outcomes in the model are discounted at 3.5%. The estimated costs, life-years and quality-adjusted life-years (QALYs) for relapsed patients with SCLC receiving topotecan plus BSC and BSC alone in the model are presented. Results are reported as incremental cost per life-year gained and incremental cost per QALY gained.

# Results

## Quantity and quality of studies

A total of 434 references were identified. Ten publications describing five randomised controlled trials (RCTs) were included in the review of clinical effectiveness. One RCT compared oral topotecan plus BSC versus BSC alone; one trial compared i.v. topotecan against CAV [cyclophosphamide, Adriamycin (doxorubicin) and vincristine]; two studies evaluated oral topotecan versus i.v. topotecan and one RCT compared i.v. topotecan with i.v. amrubicin. Assessment of methodological reporting and quality varied between the included studies. In three trials the risk of selection bias was uncertain due to a lack of reporting of the methods of generating the randomisation sequence and allocation concealment, while there was a risk of detection bias in all of the studies. Overall, methodological quality was judged to be good in two trials and unknown in three trials. For two trials, uncertainty remains as to whether the included participants fully met the licensed indication for topotecan and, as such, caution is needed when interpreting the results as the population groups may be slightly different than those eligible for topotecan according to the marketing authorisation.

Systematic searches identified no fully published economic evaluations of oral or i.v. topotecan for the treatment of relapsed SCLC in patients who were not considered appropriate for re-treatment with their first-line regimen, and only limited information on QoL/utilities in patients with relapsed SCLC. The manufacturer's submission (MS) in support of topotecan, which included an economic evaluation of oral topotecan plus BSC compared with BSC alone, was reviewed.

## Summary of clinical effectiveness

There were no statistically significant differences between groups when i.v. topotecan was compared with either CAV or oral topotecan for overall response rate (ORR), the primary outcome in four RCTs. Response rate was seen to be significantly better in participants receiving i.v. amrubicin compared with i.v. topotecan (38% versus 13%, respectively, $p = 0.039$), although it should be noted that the dose of topotecan used (1.0 mg/m$^2$) was lower than the UK recommended dose (1.5 mg/m$^2$). In the trial assessing oral topotecan against BSC, response was measured only in those in the topotecan group, as measurement of this outcome in the comparator (BSC alone) was not appropriate. Where reported, there were no statistically significant differences in TTP for i.v. topotecan compared with either CAV or oral topotecan.

In one RCT with overall survival (OS) as the primary outcome, there was a statistically significant benefit in favour of oral topotecan plus BSC compared with BSC alone [median difference 12 weeks; HR 0.61, 95% confidence interval (CI) 0.43 to 0.87, $p = 0.01$]. None of the remaining four RCTs showed any statistically significant differences in OS between treatment arms.

Only two trials measured QoL as a secondary outcome. QoL data showed a smaller decline in health status for those receiving topotecan in addition to BSC, although these results should be viewed with caution owing to issues surrounding the data reported. One of the trials comparing oral versus i.v. topotecan reported no statistical differences between groups, although no data were presented.

Generally, rates of adverse events were observed to be comparable across treatments in the included studies. Some haematological toxicities occurred significantly more frequently in the topotecan group compared with CAV, whereas rates of

haematological toxicities in the topotecan versus amrubicin trial varied between arms. Toxicities observed with oral and i.v. topotecan were similar. Rates of adverse events and toxicities were not tested for statistical significance in the studies.

### Summary of costs

Drug acquisition costs for four cycles of treatment (the mean number of cycles in trials of oral and i.v. topotecan), assuming a patient BSA of 1.8 $m^2$, were estimated at £2550 for oral topotecan and £5979 for i.v. topotecan. Non-drug treatment costs (for chemotherapy administration and monitoring while on treatment) accounted for an additional £1097 for oral topotecan [30% of total treatment costs, of which £743 (68%) is for chemotherapy administration] and £4289 for i.v. topotecan [42% of total treatment costs, of which £3936 (92%) is for chemotherapy administration].

Further costs are associated with the management of adverse events, which amount to £1584 for oral topotecan (30% of total treatment cost) and £1149 for i.v. topotecan (10% of total treatment cost). In both cases the majority of adverse event costs are associated with haematological toxicity.

### Summary of cost-effectiveness

The manufacturer's economic model, based on individual patient data from one RCT, compared oral topotecan plus BSC with BSC alone. The QALY gain with oral topotecan plus BSC was estimated at 0.211 in the base-case analysis. The cost difference was £5671, giving an incremental cost-effectiveness ratio (ICER) of £26,833 per QALY gained. Subgroup analyses suggested that oral topotecan may be more cost-effective in patients whose TTP from prior therapy was ≤ 60 days, in women and in those patients without liver metastases. Treatment with oral topotecan plus BSC also appeared to be more cost-effective for patients with a performance status of 2, as opposed to those with performance status of 0 or 1.

In the independent model the gain in discounted life expectancy associated with the addition of oral topotecan to BSC was 0.33 years (approximately 16.9 weeks) and the discounted QALY gain was 0.1830 QALYs. The incremental cost was approximately £6194, resulting in an ICER of £33,851 per QALY with the addition of oral topotecan to BSC.

The gain in discounted life expectancy associated with i.v. topotecan, compared with BSC, in the independent model was 0.30 years (approximately 15.9 weeks) – 1 week shorter than the base-case analysis for oral topotecan. The discounted QALY gain is between 0.1628 and 0.1910 QALYs, depending on assumptions regarding TTP, while the incremental cost is approximately £12,000, resulting in an ICER between £65,507 and £74,074 per QALY gained, for i.v. topotecan compared with BSC. Compared with oral topotecan, i.v. topotecan is strictly dominated or is associated with a very high ICER.

### Sensitivity analyses

In a deterministic sensitivity analysis using the manufacturer's model, the results were sensitive to methods of estimating QoL, drug administration costs and adverse event costs. Using a parametric cost-effectiveness acceptability curve, the MS reported a probability of oral topotecan plus BSC being cost-effective, compared with BSC alone, of 22% at a willingness to pay (WTP) threshold of £20,000 per QALY and 60% at a WTP threshold of £30,000 per QALY.

In a deterministic sensitivity analysis using the independent model, the cost-effectiveness results for oral topotecan plus BSC were generally robust to variation in parameters values. The results were most sensitive to assumptions over the form of survival functions adopted and variation in values of parameters in the survival functions, variation in utility estimates applied in the model and the cost of outpatient attendance for the administration of oral chemotherapy. In a probabilistic sensitivity analysis the probability of oral topotecan plus BSC being cost-effective, compared with BSC alone, was estimated at 0% using a WTP threshold of £20,000 and a 20% probability using a WTP threshold of £30,000 per QALY. A probabilistic sensitivity analysis for i.v. topotecan showed zero or very low probability of being cost-effective, compared with BSC alone, at WTP thresholds up to £50,000.

## Conclusions

In summary, the clinical evidence indicates that topotecan is better than BSC alone in terms of improved survival, is as effective as CAV, and less favourable than i.v. amrubicin in terms of response. Oral topotecan and i.v. topotecan were shown to be similar in efficacy. It remains uncertain whether topotecan is more or less toxic than comparator interventions.

The cost-effectiveness analysis showed that, for patients with relapsed SCLC, topotecan offers additional benefit over BSC, but at increased cost. Costs for i.v. topotecan are substantially higher than for oral topotecan, while health benefits are largely equivalent. ICERs for i.v. topotecan, compared with BSC, are high and suggest that it is unlikely to be a cost-effective option for this group of patients. Oral topotecan is associated with a lower ICER than BSC, although this remains at the upper extreme of the range conventionally regarded as cost-effective from an NHS decision-making perspective. Sensitivity analyses suggest the exact value of the ICER is highly dependent on assumptions regarding QoL for patients with relapsed SCLC and who are receiving oral topotecan.

## Recommendations for further research

It is unlikely that any further RCTs of topotecan compared with BSC will be ethically acceptable, nor is it likely for there to be a need to undertake a further comparison with CAV therapy, and there is little to be gained from undertaking further evidence of the effectiveness of intravenous versus oral topotecan. However, given the ongoing RCTs of topotecan versus amrubicin it would be desirable to update the current review when these report.

Further research is required into the QoL of patients with relapsed SCLC, to identify the impact of disease progression on QoL. In the case of patients receiving active treatment, further research is required on the impact of response [complete response (CR) or partial response (PR)] and the impact of treatment-related adverse events on QoL.

Further research on the impact of active treatment on resource use for palliative care would improve cost-effectiveness models for topotecan. Data collection on resource use in the RCT by O'Brien and colleagues was not comprehensive. It is difficult to determine whether the lower proportion of patients receiving radiotherapy and palliative medication (in the topotecan plus BSC arm) indicates a genuine reduction in palliative care interventions or a postponement until disease progression occurs.

## Publication

Loveman E, Jones J, Hartwell D, Bird A, Harris P, Welch K, *et al.* The clinical effectiveness and cost-effectiveness of topotecan for small cell lung cancer: a systematic review and economic evaluation. *Health Technol Assess* 2010;**14**(19).

# NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 08/36/01. The protocol was agreed in September 2008. The assessment report began editorial review in May 2009 and was accepted for publication in August 2009. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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ISSN 1366-5278



Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by Henry Ling Ltd, The Dorset Press, Dorchester.