NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Topotecan for the treatment of small-cell lung cancer

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members before the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. To allow sufficient time for the overview to be circulated to Appraisal Committee members before the meeting, it is prepared before the Institute receives consultees' comments on the assessment report. These comments are therefore not addressed in the overview.

A list of the sources of evidence used in the preparation of this document is given in appendix A.

1 Background

1.1 The condition

Lung cancer can be categorised into four major cell types: small-cell lung cancer, squamous-cell carcinoma, adenocarcinoma and large-cell carcinoma. The last three types are usually described as non-small-cell lung cancer. Small-cell lung cancer grows rapidly and spreads quickly to distant sites (metastases). It is classified using a two-stage system. The first is limited-stage disease, in which the disease is generally confined to one side of the chest or to the neck lymph nodes. The second is extensive-stage disease, in which the disease has spread beyond the thorax and there are systemic metastases. The tumour node metastases stage scores are not usually relevant in small-cell lung cancer because of the high proportion of patients presenting with metastases and the disease's poor survival.

Lung cancer is one of the most common cancers in England and accounted for 15% of cancers in men and 11% of cancers in women in 2005. There were 33,181 new cases of lung cancer in England and Wales in 2005 and the disease accounts for around 33,000 deaths per year in England and Wales. It

is estimated that small-cell lung cancer makes up about 10–20% of the total cases of lung cancer, but this percentage is falling. The reasons for this are unclear, but it has been attributed to changing smoking habits and a reduction in the tar content of cigarettes. Around 24% of people with small-cell lung cancer have limited-stage disease at diagnosis, while the remainder have extensive-stage disease.

In most patients, the disease is symptomatic on presentation. In some, there are non-specific symptoms such as fatigue, anorexia and weight loss, while in others there are more direct symptoms such as breathlessness, chest discomfort and haemoptysis (blood-stained sputum). Small-cell lung cancer is frequently associated with distinct paraneoplastic syndromes. These syndromes are not related to direct invasion of adjacent tissues by the cancer or its metastases but are caused by the release of bioactive substances produced by the tumour or in response to the tumour, for example, neurological or endocrine syndromes. The risk factors for lung cancer include smoking, passive smoking, occupational exposure to asbestos, radon, chromium and nickel, male gender and chronic lung disease. A diet rich in fruit and vegetables is associated with a reduced risk of lung cancer. Smoking is the leading cause of lung cancer, accounting for approximately 80–90% of cases. Smoking has been shown to be much more strongly linked to small-cell lung cancer than non-small-cell lung cancer.

Lung cancer is usually suspected on the basis of an initial clinical assessment, taking into account the patients' symptoms, history and a physical examination, in addition to an abnormal chest X-ray. The diagnosis is confirmed using histological and cytological tests. Patients with small-cell lung cancer are generally staged by clinical evaluation and computerised tomography of the chest and abdomen.

The prognosis for people with small-cell lung cancer is poor. Without treatment, it has an aggressive clinical course with a life expectancy of approximately 3.5 months for limited-stage disease and 6 weeks for extensive-stage disease. The median survival with treatment is approximately

14–18 months for limited-stage disease and 9–12 months for extensive-stage disease. Approximately 20–40% of patients with limited-stage disease and fewer than 5% of patients with extensive-stage disease survive 2 years. Survivors often continue to relapse up to, and occasionally after, 5 years. Prognosis has been linked to performance status and extent of disease, among other factors.

1.2 Current management

Selection of the most appropriate first-line treatment for small-cell lung cancer is determined primarily by the stage of the disease. Current management of small-cell lung cancer usually consists of combination chemotherapy regimens. Radiotherapy may be given concurrently with chemotherapy or as part of palliative care. Surgery is not appropriate for the majority of patients because the disease is often widespread at the time of diagnosis.

'Lung cancer: the diagnosis and treatment of lung cancer' (NICE clinical guideline 24) advises that:

- All patients with small-cell lung cancer should be offered platinum-based chemotherapy as part of a multidrug regimen.
- Four to six cycles of chemotherapy should be offered to patients whose disease responds. Maintenance treatment is not recommended.
- Patients with limited-stage small-cell lung cancer should be offered thoracic irradiation concurrently with the first or second cycle of chemotherapy or following completion of chemotherapy if there has been at least a good partial response within the thorax.
- Patients with limited disease and complete or good partial response after primary treatment should be offered prophylactic cranial irradiation.
- For patients with extensive disease, thoracic irradiation should be considered following chemotherapy if there has been a complete response at distant sites and at least a good partial response within the thorax.

- Second-line chemotherapy should be offered to patients at relapse only if their disease responded to first-line chemotherapy.

Platinum-based treatment combinations that are offered for first-line therapy are cisplatin or carboplatin in combination with etoposide. Other active agents include anthracyclines (doxorubicin, epirubicin), alkylating agents (cyclophosphamide, ifosfamide), vinca alkaloids (vindesine, vincristine) and taxanes (paclitaxel).

Second-line treatment depends on the response to first-line therapy and the duration of that response. Objective tumour response is assessed by X-ray or CT scan. A response requires a reduction in the tumour by at least 30% using a unidimensional measure such as the response evaluation criteria in solid tumours (RECIST), or a reduction of 50% using a bidimensional measure (World Health Organisation), and which is maintained for at least 4 weeks. Small-cell lung cancer can be categorised as treatment sensitive, resistant or refractory, according to the duration of response:

- Sensitive refers to a tumour response of more than 90 days.
- Resistant refers to tumour recurrence within 90 days.
- Refractory refers to tumours that either never responded or progressed during first-line therapy.

It is generally thought that those with treatment-sensitive disease will have the greatest benefit from second-line therapy.

Around 60–90% of patients with limited-stage disease respond to first-line therapy and 40–70% of patients achieve a complete response (no further evidence of disease). Approximately 50–85% of patients with extensive-stage disease respond to first-line chemotherapy.

2 The technology

Table 1 Summary description of technology

Non-proprietary name	Topotecan (intravenous)	Topotecan (oral)
Proprietary name	Hycamtin	Hycamtin
Manufacturer	GlaxoSmithKline	GlaxoSmithKline
Dose	1.5 mg/m^2 30-minute infusion for 5 consecutive days 21-day cycle	2.3 mg/m^2/day for 5 consecutive days 21-day cycle
Acquisition cost ('British national formulary', edition 57)	1 mg vial £97.65 4 mg vial £290.62	1 mg £30 Available as: 250 micrograms 10-capsule pack £75.00 1 mg 10-capsule pack £300.00
Cost per cycle (assuming body surface area of 1.8 m^2)	£1495	£638

Topotecan acts by inhibiting topoisomerase I, an enzyme that is required for DNA replication, leading to cell death. Topotecan is indicated as monotherapy for patients with relapsed small-cell lung cancer for whom re-treatment with the first-line regimen is not considered appropriate. The marketing authorisation for this indication was granted by the EMEA in 2006 for intravenous therapy, and an extension to the marketing authorisation was granted in 2008 for oral capsules.

If tolerated, treatment with topotecan may continue until disease progression. The advantage of oral topotecan is that it does not need specialist preparation and can be self-administered at home. Intravenous topotecan is administered in secondary or tertiary care settings, usually on a day-case basis.

As with other anti-cancer therapies, topotecan can cause severe myelosuppression, which can lead to sepsis. Other potential adverse effects include nausea and vomiting, diarrhoea, alopecia and fatigue. Rarely, topotecan causes life-threatening neutropenic colitis.

3 The evidence

3.1 Clinical effectiveness

3.1.1 Introduction

The Assessment Group reviewed the clinical effectiveness of topotecan (oral and intravenous) compared with best supportive care or other chemotherapy regimens for the second-line treatment of small-cell lung cancer. Five randomised controlled trials (RCTs) appeared to meet the inclusion criteria of the review. Three of these trials (O'Brien et al., van Pawel et al. 2001 and van Pawel et al. 1999) met the inclusion criteria, which were that re-treatment with the original first-line chemotherapy was not appropriate for reasons such as contraindication, toxicity or refusal. It was unclear whether patients in the remaining two trials (Eckardt et al. 2007 and Inoue et al. 2008) had disease that fully met the licensed indication for topotecan. Despite the uncertainties, these two studies were included in the review, although the Assessment Group emphasised the need for caution when interpreting the results. Table 2 summarises the five trials included in the review.

Table 2 Studies included in the review

Study	Intervention	Comparator	Population	Primary outcome
O'Brien et al. 2006	Oral topotecan + BSC 2.3 mg/m^2/day on days 1–5 every 21 days (n = 71)	BSC alone (n = 70)	Limited- or extensive-stage SCLC, further intravenous chemotherapy considered unsuitable	Overall survival
von Pawel et al. 1999	Intravenous topotecan 1.5 mg/m^2/day for 5 days every 21 days (n = 107)	CAV cyclophosphamide 1000 mg/m^2 (max. 2000 mg), doxorubicin 45 mg/m^2 (max. 100 mg), and intravenous vincristine 2 mg every 21 days	Limited- or extensive-stage SCLC with the date of progression 60 days or longer after completion of first-line therapy	Response rate and duration of response
Eckardt et al. 2007	Oral topotecan 2.3 mg/m^2/day on days 1–5 every 21 days (n = 155)	Intravenous topotecan 5 mg/m^2/day 30 min infusion for 5 days every 21 days (n = 154)	Limited- or extensive-stage relapsed SCLC with complete or partial response to first-line therapy and disease recurrence after 90 days or longer	Response rate
von Pawel et al. 2001	Oral topotecan 2.3 mg/m^2/day on days 1–5 every 21 days (n = 52)	Intravenous topotecan 1.5 mg/m^2/day for 5 days every 21 days (n = 54)	Limited- or extensive-stage relapsed SCLC with complete or partial response to first-line therapy and relapse after 90 days or longer	Response, response duration, time to progression
Inoue et al. 2008	Intravenous topotecan 1.0 mg/m^2/day on days 1–5 every 3 weeks (n = 30)	Intravenous amrubicin 40 mg/m^2/day on days 1–3 every 3 weeks (n = 29)	Previously platinum-treated patients who relapsed within 90 days or 90 days or longer after completion of first-line therapy	Overall response rate

BSC, best supportive care; CAV, cyclophosphamide, doxorubicin and vincristine; SCLC, small-cell lung cancer.

The reporting and methodological quality varied between the trials. Overall, methodological quality was judged to be good in two trials (O'Brien et al. 2006 and von Pawel et al. 1999) and unknown in three trials (Eckardt et al. 2007, Inoue et al. 2008 and von Pawel et al. 2001).

3.1.2 Oral topotecan compared with best supportive care

One trial (O'Brien et al. 2006) compared topotecan in combination with best supportive care with best supportive care alone. It was an international RCT in patients with limited- or extensive-stage small-cell lung cancer for whom further intravenous chemotherapy was considered unsuitable (n = 141). For further details of the patient characteristics, please see table 2, page 28 of the assessment report. The primary outcome was overall survival. The main results of this study are reported in table 3 below.

Secondary outcomes included response rate, time to progression, patient symptom assessment scale (evaluates the degree to which patients experience nine symptoms, rating from 1 [no symptoms] to 4 [very severe symptoms]), quality of life (measured by the EQ-5D) and safety. EQ-5D results were expressed as the rate of deterioration every 3 months; no baseline scores were presented. Baseline questionnaires were completed by 68 (96%) patients in the trial treated with topotecan and 65 (93%) patients in the trial receiving best supportive care alone. At least one post-baseline questionnaire was completed by 63 (89%) patients in the trial treated with topotecan and 49 (70%) patients in the trial receiving best supportive care only.

Table 3 Main results from O'Brien et al. 2006

	Treatment		p-value
	Topotecan + BSC (n = 71)	**BSC (n = 70)**	
Overall survival, median (weeks)	25.9 (95% CI 18.3 to 31.6)	13.9 (95% CI 11.1 to 18.6)	NR
6-month survival rate (%)	49	26	NR
EQ-5D, rate of deterioration per 3-month interval	−0.05 (95% CI −0.11 to 0.02)	−0.20 (95% CI −0.27 to −0.12)	Difference 0.15 (95% CI 0.05 to 0.25)
EQ-5D index (pooled analysis[a]), mean change from baseline	−0.03	−0.12	Difference 0.09 p = 0.0036
EQ-5D index (change[b]), mean change from baseline	−0.10	−0.30	Difference 0.2 p = 0.0034
EQ-5D VAS (pooled analysis[a]), mean change from baseline	0.30	−7.41	Difference 7.71 p < 0.0001
EQ-5D VAS (change[b]), mean change from baseline	−3.98	−14.46	Difference 10.48 p = 0.0025

BSC, best supportive care; CI, confidence interval; NR, not reported; VAS, visual analogue scale.

[a]Change from baseline to averaged on-treatment assessments; [b]change from baseline to last evaluation analysis.

Using Kaplan-Meier analysis, the hazard ratio for overall survival was 0.64 (95% confidence interval [CI] 0.45 to 0.90) in favour of topotecan. Drop-out rates were 30% in patients receiving topotecan in combination with best supportive care and 47% in patients receiving best supportive care alone. The number of patients receiving chemotherapy after the trial was similar between the treatment arms: 18.6% for topotecan in combination with best supportive care and 18.3% for best supportive care alone.

The overall response rate was measured in 60 of the 71 patients in the trial randomised to topotecan combined with best supportive care and was reported to be 7% (95% CI 2.33 to 15.67). Median time to disease progression was 16.3 weeks (95% CI 12.9 to 20.0) in this group.

The results of the patient symptom assessment scale suggested that shortness of breath (odds ratio [OR] 2.18, 95% CI 1.09 to 4.38), sleep disturbance (OR 2.16, 95% CI 1.15 to 4.06) and fatigue (OR 2.29, 95% CI 1.25 to 4.19) are likely to be statistically significantly improved in those patients treated with topotecan compared with those patients treated with best supportive care alone (all $p < 0.05$). It is unclear whether the patient symptom assessment scale has been validated, therefore the results should be interpreted with caution.

Rates of adverse events appeared to be similar between the two patient groups (statistical significance was not reported). Treatment-related toxicity for the topotecan arm was reported; 61% of patients had grade 3 or 4 neutropenia, 3% had febrile neutropenia, 38% had grade 3 or 4 thrombocytopenia, and 25% had anaemia.

3.1.3 Oral topotecan compared with intravenous topotecan

Two trials compared oral and intravenous topotecan. Both trials (Eckardt et al. 2007 and von Pawel et al. 2001) were international RCTs in patients with limited- or extensive-stage relapsed small-cell lung cancer who had complete response or partial response to first-line therapy with disease recurrence after 90 days or longer (n = 309 and n = 106 respectively). For further details on patient characteristics, please see table 2, pages 29–31 of the assessment report. The primary outcome for the Eckardt et al. (2007) trial was response rate, with secondary outcomes including time to response, response duration, time to progression, overall survival, toxicities and health-related quality of life (using the validated functional assessment of cancer therapy-lung scale [FACT-L] and the trial outcome index). The primary outcomes for the von Pawel et al. (2001) trial were response, response duration and time to progression. Secondary outcomes included time to progression, overall survival, symptoms and toxicities.

As shown below in table 4, there were no statistically significant differences in overall survival or overall response rate between oral and intravenous topotecan in either of the trials. In the Eckardt et al. (2007) study, post-study

monitoring showed similar proportions of patients in each group received third-line chemotherapy (33% for oral and 35% for intravenous topotecan). It is not clear whether this had an impact on the overall survival rates presented. In the von Pawel et al. (2001) study, the median overall survival for patients treated with oral topotecan was higher than those treated with intravenous topotecan but the difference was not statistically significant. After adjusting for all prognostic factors, the risk ratio of survival (oral:intravenous) was 0.90 (95% CI 0.55 to 1.47).

Health-related quality of life was assessed in the Eckardt et al. (2007) study. The mean change from baseline indicated no statistical difference between treatment groups for sub-scale dimension scores or the lung-cancer scale (LCS), the trial outcome index or the FACT-L total scores.

No statistical analyses of adverse events were reported in either study. Associated grade 3 and 4 toxicities were similar between intravenous topotecan and oral topotecan in the studies, with the exception of grade 3 or 4 neutropenia which appeared to occur more frequently with intravenous topotecan.

Neither study was powered to test for equivalence or non-inferiority. The studies were of unknown methodological quality because of the lack of details reported and there was also some uncertainty as to whether the Eckardt et al. (2007) study fully met the inclusion criteria for the review. For these reasons, it was not considered appropriate to combine the trials in a meta-analysis.

Table 4 Main results from Eckardt et al. 2007 and von Pawel et al. 2001

	Treatment		p-value
Eckardt et al. 2007	**Oral topotecan (n = 153)**	**Intravenous topotecan (n = 151)**	
Median overall survival in weeks (range) 95% CI	33.0 (0.3 to 185.3)[a] 29.1 to 42.4	35.0 (0.7 to 205.3)[a] 31.0 to 37.4	Hazard ratio = 0.98, p = ns 0.77 to 1.25
Survival rate (%): At year 1 At year 2	 33 12	 29 7	NR
Overall response rate (%) 95% CI Complete response Partial response	18.3 12.2 to 24.4 1.3 17.0	21.9 15.3 to 28.5 0 21.9	Difference −3.6 −12.6 to 5.5
Median time to response in weeks (range)	n = 28 6.1 (4.4 to 17.7)	n = 33 6.1 (2.1 to 13.9)	NR
Median response duration in weeks (range)	n = 28 18.3 (9.0 to 65.4)	n = 33 25.4 (8.4 to 132.1)[a]	NR
Median TTP in weeks (range) 95% CI	11.9 (0.3 to 149.0)[a] 9.7 to 14.1	14.6 (0.7 to 177.9)[a] 13.3 to 18.9	NR
von Pawel et al. 2001	**Oral topotecan (n = 52)**	**Intravenous topotecan (n = 54)**	
Median overall survival in weeks (range)	32.3 (0.4 to 69.1)[a]	25.1 (0.6 to 65.1)[a]	Risk ratio 0.84 95% CI 0.53 to 1.32
Overall response rate (%) 95% CI Complete response Partial response	23.1 11.6 to 34.5 1.9 21.2	14.8 5.3 to 24.3 3.7 11.1	Difference 8.3 −6.6 to 23.1
Median response duration in weeks	n = 12 18	n = 8 14	NR
Median TTP in weeks (range)	15 (0.4 to 69.1)	13 (0.6 to 65.1)[a]	Risk ratio 0.90 (95% CI 0.59 to 1.39)

CI, confidence interval; NR, not reported; TTP, time to progression.

[a] Includes censored events.

3.1.4 Intravenous topotecan compared with CAV

One trial (von Pawel et al. 1999) compared intravenous topotecan with CAV (cyclophosphamide, doxorubicin and vincristine). It was an international RCT in patients with progressive, limited- or extensive-stage small-cell lung cancer with the date of progression 60 days or longer after completion of first-line therapy (n = 211). For further details on patient characteristics, please see table 2, page 29 of the assessment report. The primary outcomes were response rate and duration of response. Secondary outcomes included time to progression, time to response, survival and improvement of disease-related symptoms. The results are summarised in table 5 below.

Table 5 Main results from von Pawel et al. 1999

	Treatment		**p-value**
	Topotecan (n = 107)	**CAV (n = 104)**	
Median overall survival in weeks (range)	25.9 (0.4 to 90.7)[a]	24.7 (1.3 to 101.3)[a]	p = 0.795
Survival rate (%): 6 months 12 months	 46.7 14.2	 45.2 14.4	NR
Overall response rate (%) 95% CI Complete response Partial response	24.3 16.2 to 32.4 0 24.3	18.3 10.8 to 25.7 1 17.3	Difference 6.0 6 to 18 p = 0.285
Median response duration in weeks (range)	n = 26 14.4 (9.4 to 50.1)	n = 19 15.3 (8.6 to 69.9)[a]	p = 0.300
Median time to response in weeks (range)	n = 26 6 (2.4 to 15.7)	n = 19 6.1 (5.4 to 18.1)	p = 0.953
Non-responders (%): Overall Stable disease Progressive disease Not assessable	 75.7 19.6 45.8 10.3	 81.7 11.5 52.9 17.3	NR
Median time to progression in weeks (range)	13.3 (0.4 to 55.1)	12.3 (0.1 to 75.3)[a]	p = 0.552

CAV, cyclophosphamide, doxorubicin and vincristine; CI, confidence interval; NR, not reported.
[a] Includes censored events.

An unvalidated, symptom-specific small-cell lung cancer questionnaire was used to measure symptoms of patients in the trials, scored on a 4-point ordinal scale (1, not at all; 2, a little bit; 3, quite a bit; 4, very much), and improvement had to be two consecutive improvements over the baseline assessment. Greater symptomatic improvement was seen in patients who received topotecan for symptoms of dyspnoea ($p = 0.002$), anorexia ($p = 0.042$), hoarseness ($p = 0.043$), fatigue ($p = 0.032$) and interference with daily activity ($p = 0.023$).

The most frequently reported adverse events were nausea, fatigue, vomiting, anorexia and alopecia. Overall, the groups appeared comparable for all reported adverse events, although the incidence of fatigue was lower and the incidence of alopecia was higher in participants receiving topotecan compared with those receiving CAV. No statistical comparison was reported. Six deaths (5.6%) in the topotecan group and four deaths (3.8%) in the CAV group were related or possibly related to treatment.

3.1.5 Intravenous topotecan compared with intravenous amrubicin

One RCT (Inoue et al. 2008) was identified that compared intravenous topotecan with intravenous amrubicin. It was conducted in Japan in patients previously treated with platinum who had relapsed within 90 days or 90 days or longer after completion of first-line therapy (n = 59). For further details on patient characteristics, please see table 2, pages 31 and 32 of the assessment report. The primary outcome was overall response rate. Secondary outcomes were progression-free survival, overall survival and toxicity profile. The main results are summarised in table 6 below.

It should be noted that the topotecan dose of 1.0 mg/m^2/day (the approved dose in Japan) was below the UK recommended dose of 1.5 mg/m^2/day. In addition, the study was of an unknown quality due to the lack of details reported in the trial.

Table 6 Main results from Inoue et al. 2008

	Treatment		p-value
	Intravenous amrubicin (n = 29)	Intravenous topotecan (n = 30)	
Overall survival, median (months)	8.1	8.4	p = 0.17
Progression-free survival, median (months)	3.5	2.2	p = 0.16
Overall response (%)	38% (95% CI 21 to 58)[a]	13% (95% CI 1 to 25)[b]	p = 0.039
CI, confidence inverval. [a]20 to 56 in abstract; [b]4 to 31 in conference presentation.			

3.2 Cost effectiveness

Systematic searches conducted by the Assessment Group identified no fully published economic evaluations of oral or intravenous topotecan for the treatment of relapsed small-cell lung cancer in patients for whom re-treatment with the first-line regimen was not considered appropriate. Limited information on quality of life/utilities was identified in patients with relapsed small-cell lung cancer.

The manufacturer of topotecan submitted an economic evaluation of oral topotecan in combination with best supportive care compared with best supportive care alone. This was reviewed by the Assessment Group. An independent model was developed by the Assessment Group to estimate the cost effectiveness of topotecan (oral or intravenous) compared with best supportive care for patients with relapsed small-cell lung cancer, for whom re-treatment with the first-line regimen was not considered appropriate.

3.2.1 Manufacturer's submission

Methods

The aim of the manufacturer's analysis was to assess the cost effectiveness of oral topotecan in combination with best supportive care compared with best supportive care alone in people with relapsed small-cell lung cancer in whom treatment with intravenous chemotherapy was not considered appropriate.

The analysis was based on patient-level data from the O'Brien et al. (2006) RCT. CAV was excluded as a comparator from the analysis on the basis that topotecan (oral or intravenous) would not provide a cost-effective alternative to CAV in the majority of patients, given its higher acquisition cost. Best supportive care in the evaluation consisted of analgesics, antibiotics, corticosteroids, appetite stimulants, antidepressants, red blood cell transfusions, deep relaxation therapy, and palliative radiotherapy or surgical procedures. The perspective was that of the NHS and personal social services (PSS), capturing only the costs and benefits directly relevant to the intervention. The submission stated that costs and outcomes (life years gained and quality-adjusted life years [QALYs] gained) for each treatment arm were estimated over a lifetime horizon. However, the time horizon used in the economic evaluation was the duration of the trial. No additional modelling was undertaken to extend survival beyond the end of the trial. An incremental analysis of topotecan in combination with best supportive care compared with best supportive care alone was undertaken.

The mean survival in the manufacturer's model was estimated directly from the survival durations for patients in the O'Brien trial. Patients who were still alive at final follow-up were assumed to have died the day after. No sensitivity analysis was conducted around this assumption. Health-related quality of life was recorded in the O'Brien trial using the EQ-5D, for up to 12 cycles (36 weeks), and valued using a UK general population tariff. Missing values were imputed using data from the trial, using the mean utility score (across both trial arms) for missing values up to cycle 12. When patients receiving topotecan survived with non-progressive disease beyond the 36-week data collection, the last observation was carried forward until disease progression occurred. Once these patients developed progressive disease, values for those receiving best supportive care alone were applied. The costs included in the model were drug acquisition costs, drug administration costs, drug monitoring costs, costs of treating haematological and non-haematological adverse events, and costs of providing care in the additional period of life attributable to oral topotecan combined with best supportive care. Not all

resource use was collected in the trial and therefore clinical opinion was used to fill in gaps in the resource use. The cost year for the model was 2007/08.

Results

In the manufacturer's base case, the incremental life years and QALYs gained for the cohort of patients receiving oral topotecan combined with best supportive care compared with those receiving best supportive care alone were estimated at 0.259 years and 0.211 QALYs gained, respectively. The incremental cost was £5671, giving an incremental cost-effectiveness ratio (ICER) of £21,878 per life year gained and £26,833 per QALY gained.

Deterministic sensitivity analysis showed that the results were sensitive to methods of estimating utility (methods of carrying forward utility scores when there were missing data), drug administration cost (significantly higher costs if a patient attended as an outpatient on 5 days of the cycle to receive chemotherapy compared with 1 day of the cycle) and adverse event costs (halving or doubling adverse event costs).

Probabilistic sensitivity analysis showed that treatment with oral topotecan plus best supportive care was almost always associated with increased costs (incremental costs between £4000 and £7500) and with increased QALYs (incremental QALYs between 0 and approximately 0.6) (in 98% of replications) compared with best supportive care alone. Cost-effectiveness acceptability curves reported in the manufacturer's submission estimated a 22% probability of oral topotecan in combination with best supportive care being cost effective at a willingness to pay threshold of £20,000 per QALY, and a 60% probability at a willingness to pay threshold of £30,000 per QALY.

Subgroup analyses showed that oral topotecan was more likely to be cost effective in patients whose time to progression from prior therapy was less than or equal to 60 days (ICER of £17,946 per QALY gained), in women (ICER of £11,708 per QALY gained) and in those patients without liver metastases (ICER of £21,291 per QALY gained). Treatment with oral topotecan in combination with best supportive care also appeared to be more cost effective for patients with a performance status of 2 (ICER of £25,544 per

QALY gained) compared with a performance status of 0 or 1 (ICER of £30,770 per QALY gained).

3.2.2 Assessment Group's economic model

The Assessment Group developed a new model, using a survival model methodology, to estimate the cost effectiveness of topotecan as a second-line treatment compared with best supportive care, in a cohort of adults with relapsed small-cell lung cancer for whom re-treatment with the first-line regimen was not considered appropriate. The model included three states: relapsed small-cell lung cancer (entry to the trial), progressive disease and death. The economic evaluation was a cost–utility analysis and the perspective was that of the NHS and PSS. The outcomes evaluated were life years and QALYs gained over the lifetime of the patients. The base-case model had a 5-year time horizon.

The scope stated that the interventions (both oral and intravenous topotecan) should be compared with each other along with best supportive care, CAV and any other chemotherapy regimens. The RCTs identified by the Assessment Group in the clinical effectiveness search (see section 3.1) highlighted different study populations for topotecan and the relevant comparators. Therefore the Assessment Group considered that it was not appropriate to pool the results. The base-case analysis of the model was limited to oral topotecan combined with best supportive care compared with best supportive care alone (based on O'Brien et al. 2006). The Assessment Group also noted that CAV was likely to be a more cost-effective option than topotecan as second-line chemotherapy for small-cell lung cancer in patients for whom CAV is not contraindicated. Therefore, topotecan would only be used in a subgroup of patients, when CAV was not considered appropriate as second-line chemotherapy. The Assessment Group also completed an analysis of intravenous topotecan compared with best supportive care, based on an indirect comparison. The Assessment Group noted that there were reservations with this analysis given the uncertainty of whether the trials fully

met the criteria for the review, the comparability of the patient populations in the RCTS and the suitability of pooling their results.

Effectiveness data

The model adopted a survival model methodology, using the published Kaplan-Meier estimates for overall survival and time to progression included in the manufacturer's submission. The final portions of the survival curves were extrapolated using a regression analysis. Different parametric survival functions were fitted to the observed Kaplan-Meier estimates. The log-logistic function provided the best fit and was used in the model. The mean survival estimated from the Kaplan-Meier survival function and from the log-logistic survival function is shown in table 7.

Table 7 Mean overall survival from Kaplan-Meier and log-logistic functions

Treatment arm	Mean overall survival (years)	
	Kaplan-Meier estimate	Log-logistic function
Oral topotecan plus BSC	0.7685	0.8271
BSC	0.4837	0.4864
BSC, best supportive care.		

Kaplan-Meier estimates for time to progression were not reported by O'Brien et al. (2006); only the median time to progression for oral topotecan combined with best supportive care was reported. No time to progression data were reported for best supportive care alone. The mean time to progression for oral topotecan combined with best supportive care was estimated using an exponential approximation to derive the risk of disease progression from the reported median time to progression (see page 68 of the assessment report). The mean time to progression was then calculated by taking the reciprocal of the risk of disease progression, giving a value of 23.52 weeks.

An adjusted indirect comparison was undertaken to assess the effect of intravenous topotecan on overall survival relative to best supportive care, using data from three RCTs included in the clinical effectiveness review (O'Brien et al. 2006, Eckardt et al. 2007 and von Pawel et al. 2001). Further

details can be found on page 69 of the assessment report. The relative risk for overall survival with intravenous topotecan was 0.68 (95% CI 0.45 to 1.02) compared with best supportive care.

The base-case model had an approximate lifetime horizon, with extrapolation of the survival up to 5 years. Deterministic sensitivity analyses investigated alternative survival scenarios (using a longer time horizon or limited to the maximum follow-up in the O'Brien RCT) to assess the impact on cost effectiveness. Alternative forms of the survival function were also investigated to assess the sensitivity of cost effectiveness to structural assumptions.

Utility data

The utility values used in the model were those reported for patients in the RCT by O'Brien et al. (2006).This was the only relevant study identified in the Assessment Group's review of quality of life data. EQ-5D scores from the trial were reported as a rate of deterioration per 3-month interval for patients in each arm in the trial, controlling for baseline utility. The baseline utility for all patients in the model was assumed to be 0.7. The reported reductions over 3 months were converted to daily utility reductions (with regression analysis) for use in the Assessment Group's model and applied to the baseline utility values in the O'Brien et al. (2006) RCT. The rate of deterioration reported for oral topotecan and best supportive care was used for patients prior to disease progression. To allow for reduced quality of life in patients following disease progression, the rate of deterioration reported for best supportive care alone was applied to oral topotecan patients who had experienced disease progression.

Resource use data

The resource use data associated with oral and intravenous topotecan were estimated from the RCTs included in the clinical-effectiveness review, the manufacturer's submission and advice from clinical experts. When insufficient detail was available (such as for palliative care), appropriate costs were taken from published sources. Drug costs were taken from the 'British national formulary', edition 56. Other unit costs were taken from NHS reference costs,

Southampton University Hospitals Trust or published sources. The cost base for the evaluation was 2007/08. Costs were inflated when taken from other cost years.

Results

The addition of oral topotecan to best supportive care resulted in a life-expectancy gain of 0.33 years (approximately 16.9 weeks) and a QALY gain of 0.1830 QALYs. The incremental cost was approximately £6200, resulting in an ICER of £33,851 per QALY gained.

Probabilistic sensitivity analysis showed that oral topotecan in combination with best supportive care had a 0% probability of being cost effective, compared with best supportive care alone, at a willingness to pay threshold of £20,000 per QALY gained. The equivalent figure for a willingness to pay threshold of £30,000 was 20%.

Intravenous topotecan was associated with a gain in life expectancy of 0.30 years (approximately 15.9 weeks) – approximately 1 week shorter than the base-case analysis for oral topotecan. The QALY gain was 0.1628, when time to progression was modelled using data from the von Pawel et al. (2001) RCT and 0.1910 when time to progression was modelled using data from the Eckardt et al. (2007) RCT. The incremental cost associated with intravenous topotecan was approximately £12,000 (£12,060 and £12,514, when time to progression was modelled using data from the RCTs by von Pawel et al. [2001] and by Eckardt et al. [2007], respectively). The resulting ICER for intravenous topotecan compared with best supportive care was between £74,074 and £65,507 per QALY gained, depending on assumptions regarding time to progression.

Compared with oral topotecan, intravenous topotecan was strictly dominated (poorer outcomes at higher cost) when time to progression was modelled using data from the von Pawel et al. (2001) RCT, while the ICER was approximately £783,734 per QALY gained when time to progression was modelled using data from the Eckardt et al. (2007) RCT.

Probabilistic sensitivity analysis showed that intravenous topotecan had a 0% probability of being cost effective, compared with best supportive care alone, at willingness to pay thresholds of £20,000 and £30,000 per QALY gained. For a willingness to pay threshold of £50,000, the equivalent figure was between 1% and 7.6%, depending on assumptions regarding time to progression.

3.2.3 Comparison of the manufacturer and Assessment Group models

The Assessment Group's survival model gave a higher estimate of mean survival than the manufacturer's model using the patient-level data. This difference was mainly due to the assumption, in the manufacturer's model, that censored patients die on the day after censoring. This appears to have a disproportionately large effect for the cohort treated with oral topotecan in combination with best supportive care, in which 1 patient was censored after a relatively short period of follow-up, but also involves truncation of the maximum survival duration when up to 5% of patients treated with oral topotecan in combination with best supportive care were still alive.

The manufacturer and the Assessment Group used different ways to estimate the utilities in the analysis. The manufacturer used the observed mean EQ-5D scores from the first 12 cycles from both arms of the trial to take account of missing data from the corresponding cycles. When patients receiving topotecan survived with non-progressive disease beyond the 36-week (12 cycles) data collection, the last observation was carried forward until disease progression occurred. Once these patients developed progressive disease, values for those receiving best supportive care alone were applied. The Assessment Group used a regression analysis to estimate the daily rate of deterioration in utility and applied this to the baseline utility values from the O'Brien et al. trial, in order to model utility beyond the last observation and beyond the trial.

The Assessment Group's base-case ICER was higher than that of the manufacturer for oral topotecan combined with best supportive care compared with best supportive care alone (£33,851 and £26,833, respectively).

4 Issues for consideration

There was no comparison of oral topotecan versus CAV provided. The manufacturer did not provide this analysis on the basis that topotecan (oral or intravenous) would not provide a cost-effective alternative to CAV in the majority of patients, given its higher acquisition cost. The Assessment Group also noted that CAV was likely to be a more cost-effective option than topotecan as second-line chemotherapy for small-cell lung cancer in patients for whom CAV is not contraindicated. Therefore, topotecan would only be used in a subgroup of patients, in whom CAV was not considered appropriate as second-line chemotherapy.

It is uncertain whether the trial populations fully meet the licensed indication for topotecan, which is for the treatment of patients with relapsed small-cell lung cancer for whom re-treatment with the first-line regimen is not considered appropriate. In addition, all of the studies included patients from countries other than the UK. Given these limitations, are the results of the studies included in the review generalisable to the UK population?

Only two RCTs reported any quality of life data, one of which reported no baseline data and only minimal information on participants included in the analysis, and the other provided no data at all. Little detail was reported in the O'Brien trial on the methods adopted for calculating utilities from the EQ-5D (the value set is not reported), how missing data was handled, or methods to estimate deterioration in scores over time. In addition, there was a limited follow-up for the quality of life assessments of 12 weeks (3 months). The quality of life data are unlikely to capture the full impact of disease progression in the oral topotecan arm. There is therefore uncertainty around the utility data included in the model. However, this uncertainty was addressed in the sensitivity analysis.

It is uncertain whether the disutility of experiencing an adverse event for patients receiving topotecan has been adequately captured due to the large amount of missing EQ-5D data and 3-week intervals between EQ-5D data collection. The utility gain for topotecan compared with best supportive care could be overestimated; healthier patients may be more willing and able to complete the EQ-5D than those experiencing an adverse event. What are the implications of this uncertainty?

The manufacturer and the Assessment Group used different approaches for the cost effectiveness analysis. The manufacturer used patient level data from the O'Brien et al. (2006) RCT whereas the Assessment Group used a survival model based on the O'Brien et al. (2006). Should the estimates for cost effectiveness be taken from the manufacturer's analysis or the Assessment Group's analysis?

5 Ongoing research

There are two ongoing trials related to this appraisal:

- NCT00319969 is a phase II, randomised controlled trial comparing IV amrubicin (40 mg/m^2) with IV topotecan (1.5 mg/m^2) in adults with extensive-stage small-cell lung cancer sensitive to first-line (platinum-based) chemotherapy. Estimated study completion date: January 2009.
- NCT00547651 is a phase III, randomised controlled trial comparing IV amrubicin (40 mg/m^2) with IV topotecan (1.5 mg/m^2) in adults with extensive-stage or limited-stage small-cell lung cancer sensitive or refractory to first-line (platinum-based) chemotherapy. Estimated study completion date: March 2011.

6 Authors

Helen Knight
Technical Lead

Janet Robertson
Technical Adviser

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Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report for this appraisal was prepared by Southampton Health Technology Assessment Centre.

- Loveman E, Jones J, Hartwell D et al. The clinical and cost effectiveness of topotecan for small cell lung cancer: a systematic review and economic evaluation, March 2009.

B Submissions or statements from the following organisations:

I Manufacturer/sponsor

- GlaxoSmithKline

II Professional/specialist, patient/carer and other groups:

- Royal College of Physicians (on behalf of NCRI/RCP/RCR/ACP/JCCO)
- Roy Castle Lung Cancer Foundation
- Royal College of Nursing

C Additional references used:

NICE Clinical Guideline No. 24, February 2005, 'Lung cancer: the diagnosis and treatment of lung cancer', [review expected, February 2009]