Scottish Medicines Consortium

topotecan 1mg, 4mg powder for concentrate for solution for infusion (Hycamtin®) No. (366/07)

GlaxoSmithKline

6 April 2007

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

topotecan (Hycamtin®) is not recommended for use within NHS Scotland for the treatment of patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate.

In a trial comparing oral topotecan plus active symptom control (ASC) to ASC alone the difference in median survival was 12 weeks, in favour of the oral topotecan plus ASC group. Topotecan is not available as an oral formulation in the UK, however in one trial the response rate and median survival duration were similar for oral and IV topotecan groups.

The treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate.

Dosing information

1.5mg/m^2 body surface area/day administered by intravenous infusion over 30 minutes daily for 5 consecutive days with a 3 week interval between the start of each course. Further doses will depend on neutrophil and platelet counts and haemoglobin levels. If well tolerated treatment may continue until disease progression.

Product availability date

13 January 2006

Summary of evidence on comparative efficacy

Topotecan is a cytotoxic anti-cancer agent which exerts its activity by the inhibition of the nuclear enzyme topoisomerase I. Three pivotal trials have investigated the use of topotecan for the treatment of relapsed SCLC. Patients were eligible if they were ≥ 18 years, had received one prior chemotherapy regimen only, and had documented partial or complete response to first-line therapy and an Eastern Co-operative Study Group (ECOG) performance status (PS) score of ≤ 2. They were also required to have documented relapse of limited or extensive SCLC at least 45, 60, 90 days after cessation of first-line chemotherapy in the first, second and third trials respectively.

The first trial recruited 141 patients who were not considered suitable for further intravenous chemotherapy, to receive either active symptom control (ASC) alone or ASC plus oral topotecan; 2.3mg/m²/day for 5 consecutive days repeated every 21 days. ASC encompasses all palliation and support modalities (including analgesics, antibiotics, corticosteroids, appetite stimulants, antidepressants, RBC transfusion, deep relaxation therapy, palliative radiotherapy or surgical procedures). The primary study objective was overall survival, defined as time from randomisation until death from any cause and secondary objectives included response rate, time to disease progression (TTP) and quality of life (measured using the EuroQOL-5 Dimension Health Questionnaire (EQ-5D), an evaluation of five health status dimensions).

The intention-to-treat population (all randomised patients) comprised 71 and 70 patients in the oral topotecan plus ASC and ASC alone groups, respectively. The median survival in the oral topotecan plus ASC group was 25.9 weeks compared to 13.9 weeks in the ASC alone group. The unadjusted hazard ratio (HR) for oral topotecan plus ASC relative to ASC alone was 0.64 (95% C.I. 0.45, 0.90), indicating a 36% reduction in the risk of death for the oral topotecan plus ASC group. In the oral topotecan plus ASC arm five patients (7.0%) had a partial response to treatment and no patients had a complete response. The rate of change over 3 months in EQ-5D was -0.05 (95% CI -0.11, 0.02) and -0.20 (95% CI -0.27, -0.12) for the oral topotecan plus ASC and ASC alone groups respectively. The median TTP for the oral topotecan plus ASC group was 16.3 weeks (95% CI 12.9, 20.0) and was not reported in the ASC alone group.

In the second trial 107 patients were treated with topotecan (1.5mg/m^2 intravenous infusion for 5 consecutive days every 21 days) and 104 patients with cyclophosphamide 1g/m^2, doxorubicin 45mg/m^2, vincristine 2mg administered intravenously on day 1, every 21 days (CAV). The primary efficacy variable was response rate defined as the percentage of

patients who had a complete or partial response, and duration of response (the time from the initial documented response to the first sign of progression). Secondary endpoints included survival and patient symptom assessment/quality of life (the following symptoms were assessed at baseline and at the end of each course of treatment; shortness of breath, cough, chest pain, coughing up blood, loss of appetite, interference with sleep, hoarseness, fatigue and interference with daily activities). The response rate for intravenous topotecan was 24.3% (95% CI 16.2, 32.4) and for CAV was 18.3% (95% CI 10.8, 25.7). The median response duration was 14.4 weeks and 15.3 weeks for topotecan and CAV respectively and the median survival was 25.0 weeks (95% CI 20.6, 29.6) for topotecan and 24.7 weeks (95% CI 21.7, 30.3) for CAV (p=0.795). There was greater symptomatic improvement for topotecan patients in the following symptoms; dyspnoea, hoarseness, anorexia, fatigue and interference with daily activity and CAV did not show significant improvement over topotecan for any symptom.

The third trial was designed to investigate the clinical profile of topotecan IV (dosing regimen as in the 2nd study) with topotecan oral (dosing regimen as in the 1st study) as second-line therapy in patients with advanced SCLC. The primary objective of the study was to evaluate the response (partial or complete response) rate and secondary objectives included survival and quality of life (assessed using the Functional Assessment of Cancer Therapy-G and Lung Cancer Subscale [FACT-L]). The ITT population comprised 153 and 151 patients in the topotecan oral and topotecan IV groups respectively. A total of 28 patients (18.3%) responded to treatment with oral topotecan versus 33 patients (21.9%) in the IV topotecan group. The percentage difference (oral minus IV) was -3.6% (95% CI -12.6%, 5.5%). At the lower non-inferiority bound of -10%, non-inferiority of oral topotecan to IV topotecan was not demonstrated for response rate. The median survival for topotecan oral was 33.0 weeks compared with 35.0 weeks for topotecan IV (HR 0.95; 95% CI 0.75, 1.21). In terms of quality of life, there was no significant difference between oral and IV treatments in change from baseline in total FACT-L scores.

Summary of evidence on comparative safety

In the trial comparing IV and oral topotecan, haematological toxicity was slightly higher for IV compared to oral topotecan; however the differences were not significant.

In the second trial grade 4 neutropenia was experienced by similar numbers of patients treated with topotecan and CAV. However, the percentage of courses that caused grade 4 neutropenia was higher in CAV treated patients (p<0.001). Grade 4 thrombocytopenia and grade 3/4 anaemia had a higher incidence in patients receiving topotecan (p<0.001 for both) compared with patients receiving CAV. There were similar rates of suspected or documented infection in both groups.

The discussion on clinical safety in the scientific discussion of the European Public Assessment Report produced by the European Medicines Agency commented that “overall there are no new safety issues for topotecan when used in relapsed SCLC as compared with relapsed ovarian cancer. It has also been shown that there are no major differences regarding safety risks with IV topotecan as compared with oral”.

Summary of clinical effectiveness issues

The company has requested that the indication for topotecan currently under review by SMC is restricted to patients in whom second-line chemotherapy is considered suitable but for whom an anthracycline-based regimen is judged to be clinically inappropriate due to serious pre-existing cardiovascular conditions or contraindications. The applicability of the trial results to the sub-group of patients with cardiovascular complications is not clear as a sub-group analysis is not possible. Expert opinion obtained by SMC indicates that the clinical benefits seen in the trial population are considered applicable to the sub-group of patients described.

In the first trial (which compared oral topotecan + ASC v ASC) patients were eligible if they were considered unsuitable for further intravenous chemotherapy. Unsuitability was based on local policy concerning unproven risk and benefit in patients with resistant (i.e. a short treatment-free interval) SCLC and assessed on an individual basis. Reasons why a patient was not considered a candidate for further IV chemotherapy were not captured fully for the trial. However, potential reasons included a very short TTP following an initial response to first line chemotherapy, a relatively short TTP from, and residual toxicity to, first-line chemotherapy, and patient preference. Therefore the patients recruited to this trial may not be representative of patients who may be eligible for intravenous topotecan. The oral formulation of topotecan is not licensed in the UK.

Summary of comparative health economic evidence

The manufacturer provided a clinical trial-based economic evaluation comparing IV topotecan plus ASC to ASC alone in patients eligible for second-line chemotherapy but who were unable to take anthracycline-based regimens due to cardiovascular contraindications. This was an appropriate comparator. Cost-effectiveness was estimated over the remaining lifetime of the patients using an indirect comparison.

To perform the economic evaluation, the company stated that information from clinical trials showed that IV and oral treatment with topotecan produced similar clinical outcomes, quality of life and safety profiles. Using this assertion, the company then assumed that the clinical outcomes seen in the oral topotecan versus ASC trial would hold true for IV topotecan versus ASC. Using this approach, IV topotecan gave an additional life year gain of 0.267 compared to ASC. These values were taken from data on the overall outcomes of the trial rather than specifically in the small subgroup of patients with cardiovascular problems. The utility values were estimated using EQ-5D scores collected in the oral topotecan clinical trial that showed that topotecan patients had better quality of life.

The results of the analysis gave an incremental cost per QALY of £21582 or £19433 per life year gained. The results were sensitive to changes in some key parameters:

- topotecan vial re-use: if all unused topotecan was discarded then the ICER rose to around £30,000 per QALY. SMC clinical experts suggested that some reuse of vials may take place depending on local facilities and practice.
- utility assumptions: removal of the baseline quality of life advantage for topetecan increased the ICER to around £27,000.

- poorer survival benefit with topotecan: a 10% less survival benefit with topotecan would increase the ICER to around £27000 per QALY. This could be important if, for example, the outcomes for patients with cardiovascular contraindications were poorer than for the average trial patient.

The combined effect of less than 100% vial re-use and changes to the utility gains increases the ICER to around £30,000. If the effect of poorer survival was added to this estimate then the cost effectiveness ratio would increase beyond £30,000.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

SIGN published guideline 80; *Management of patients with lung cancer* in February 2005. The guideline states that "second line chemotherapy in patients with SCLC should be considered depending on the duration of response to first line chemotherapy and on patients' performance status and wishes".

The National Institute for Health and Clinical Excellence published a guideline entitled; *Lung cancer- The diagnosis and treatment of lung cancer* in February 2005. It states that "second-line chemotherapy should be offered to patients at relapse only if their disease responded to first-line chemotherapy. The benefits are less than those of first-line chemotherapy".

Both guidelines predate the availability of topotecan for the indication under review.

Additional information: comparators

For the restricted indication (where second line chemotherapy is considered suitable but for whom an anthracycline-based regimen is judged to be clinically inappropriate due to serious pre-existing cardiovascular conditions or contraindications) there are no comparators.

Additional information: costs

Product	Regimen	Cost *per course (£)
topotecan	**1.5mg/m^2/day for days 1 to 5, repeated every 21 days.**	**1453**

* Cost of topotecan vials taken from BNF number 52 (September 2006), based on a surface area of 1.8m^2 and have assumed wastage of remaining contents of vial.

Additional information: budget impact

The manufacturer estimated a budget impact of £78k per year, assuming no drug wastage. This estimate included drug acquisition costs and the costs associated with administration of IV topotecan. The company assumed that 29 patients would be eligible for treatment and of these patients, 50% would take up this treatment option- a total of 15 patients per year.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 20 March 2007.

Costs in the 'Cost of relevant comparators' section are based on prices available at the time the papers were issued to SMC for consideration. Further details are available on the SMC web site at http://www.scottishmedicines.org.uk/updocs/Costing%20FAQs.pdf

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

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European Medicines Agency. Scientific Discussion (EMEA/H/C/123/II/34). 6 January 2006. Accessed on 17/1/06.
http://www.emea.europa.eu/humandocs/Humans/EPAR/hycamtin/hycamtin.htm