Horizon Scanning Technology Summary

Oral topotecan (Hycamtin) for small cell lung cancer

April 2007

This technology summary is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes.
Oral topotecan (Hycamtin) for small cell lung cancer

Target group
- Relapsed small cell lung cancer (sclc) - treatment-resistant and treatment-sensitive

Technology description
An oral formulation of topotecan (Hycamtin) is in development for the treatment of relapsed small cell lung cancer. Topotecan acts by inhibiting topoisomerase I inhibitor, an enzyme that is required for DNA replication, leading to cell death. The recommended dose of oral topotecan is 2.3 mg/m²/day, administered for 5 consecutive days, in 21-day cycles.

Oral topotecan is in phase III trials in combination with whole brain radiation therapy for non-small cell lung cancer.

Intravenous topotecan is already licensed for the treatment of relapsed small cell lung cancer, and as a second-line treatment for ovarian cancer, and as a combination therapy with cisplatin for patients with carcinoma of the cervix, either recurrent after radiotherapy or for stage IVB disease.

Innovation and/or advantages
Oral topotecan may be self-administered and does not require the specialist preparation and administration needed for the intravenous formulations. Oral topotecan administered on an outpatient basis is associated with a high degree of patient compliance.

Developer
GlaxoSmithKline.

Place of use
- ☑ Secondary care e.g. general, non-specialist hospital
- ☐ General public e.g. over the counter
- ☐ Community or residential care e.g. district nurses, physio
- ☐ Tertiary care e.g. highly specialist services or hospital
- ☐ Other
- ☐ Primary care e.g. used by GPs or practice nurses
- ☐ Emergency care e.g. paramedic services, trauma care

Availability, launch or marketing dates, and licensing plans:
Oral topotecan for the indication of relapsed sclc is in phase III clinical trials.

NHS or Government priority area:
- ☑ Cancer
- ☐ Cardiovascular disease
- ☐ Children
- ☐ Diabetes
- ☐ Chronic conditions
- ☐ Mental health
- ☐ Older people
- ☐ Public health
- ☐ Renal disease
- ☐ Women's health
- ☐ None identified
- ☐ Other

This topic relates to the National Service Framework for Cancer: The NHS Cancer Plan (published, September 2000).

Relevant guidance


NICE. Technology appraisals in development for non-small cell lung cancer: erlotinib; erlotinib and pemexreted; pemexreted (expected completion, Spring 2007).


Clinical need and burden of disease

In 2003, lung cancer was the second most common cancer in men and third most common cancer in women, accounting for 31,900 new cases of lung cancer in England and Wales\(^2\). Small cell lung cancer constitutes about 20-25% of all lung cancers\(^3\),\(^4\), an estimated 6,380 to 7,975 of the new cases. Of these, around 30 to 40% are classed as limited stage at diagnosis (tumour confined to one side of the chest or to the neck lymph nodes), while the remainder have extensive stage disease (defined as the presence of obvious metastatic disease)\(^5\),\(^6\).

Sclc usually spreads very quickly to other parts of the body\(^7\). The initial response rate to chemotherapy is estimated as 45-75% with complete remission for those with limited-stage disease, and 20-30% for those with extensive disease\(^8\). However the response duration is short with median progression-free survival for patients with limited-stage disease of approximately 12 months, and 4 months for patients with extensive-stage disease\(^8\).

Expert opinion varies but it is estimated that treatment with oral topotecan may be appropriate for around 25-50% of all sclc patients who received 1\(^{st}\) line therapy.

Existing comparators and treatments

Chemotherapy is the main treatment option for small cell lung cancer. The NICE lung cancer clinical guideline\(^9\) advises that:

- All patients with newly diagnosed sclc should be offered a platinum-based chemotherapy, and multi-drug regimes.
- Patients with limited-stage sclc 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.
- 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.

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial name or code</th>
<th>Oral topotecan vs. best supportive care (BSC) in relapsed and resistant sclc</th>
<th>Oral vs. iv topotecan in relapsed sclc</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>GSK</td>
<td>GSK</td>
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<tr>
<td>Status</td>
<td>Published¹³</td>
<td>Abstract and slides¹⁴, Company release¹²</td>
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<tr>
<td>Location</td>
<td>Europe (inc. UK), Canada, Russia.</td>
<td>International (including UK).</td>
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<tr>
<td>Design</td>
<td>Phase III, randomised, active control, open label</td>
<td>Phase III, randomised, stratified by prognostic factors</td>
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<tr>
<td>Participants in trial</td>
<td>n=141. Patients with extensive or limited sclc, who have relapsed after one prior chemotherapy regime (but with a complete partial response to first-line therapy), and who are not considered candidates for further standard iv therapy. Arm I – Oral topotecan plus BSC: n=71, oral topotecan 2.3 mg/m²/day, days 1 through 5, every 21 days. Arm II – BSC: n=70.</td>
<td>n=304. Patients with limited or extensive sclc, and a documented partial or complete response to first-line therapy (and who had only received one prior chemotherapy regime), with recurrence of disease at least 90 days following cessation of first-line therapy. Arm I - Oral topotecan: n=153, 2.3 mg/m²/day for 5 days every 21 days. Arm II - IV topotecan: n=151, 1.5 mg/m²/day for 5 days, every 21 days. Patients stratified according to gender, liver metastases, and duration of response to prior chemotherapy. Therapy continued for a minimum of 4 courses, unless there was early disease progression or unacceptable toxicity. There was no upper limit on the number of treatment cycles.</td>
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<tr>
<td>Follow-up</td>
<td>Every two months until death</td>
<td>Every 3 months</td>
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<td>Primary outcome</td>
<td>Overall survival</td>
<td>Non-inferiority of response rate of oral compared to iv topotecan</td>
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<tr>
<td>Secondary outcomes</td>
<td>Time to response; response rate; time to disease progression</td>
<td>Response duration; time-to-response; time-to-progression; survival; quality of life; toxicities</td>
</tr>
<tr>
<td>Key results</td>
<td>Median treatment free interval: topotecan 84 days; BSC 90 days. Median survival: Topotecan 25.9 weeks (95%CI, 18.3-31.6); BSC 13.9 weeks (95%CI, 11.1-18.6), p=0.0104 Six month survival rates: Topotecan 49%; BSC 26%. All cause mortality within 30 days of randomisation Topotecan 7%; BSC 13%</td>
<td>Total responders (complete and partial): Oral n=28, 18.2% (95%CI, 12.2-24.4); iv n=33, 21.9% (95%CI, 15.3-28.5); difference -3.6 (95%CI, -12.6%-5.5%) Time to response (median): Oral 6.1 weeks (range, 4.4-17.7); iv 6.1 weeks (range 2.1-13.9) Response duration (median): Oral 18.3 weeks (range, 9.0-65.4); iv 25.4 weeks (range, 8.4-132.1) Time to progression (median): Oral 11.9 weeks (95%CI, 9.7-14.1; range, 0.3-94.7); iv 14.6 weeks (95%CI, 13.3-18.9; range, 0.7-137.6); hazards ratio=1.32 (95%CI, 1.04-1.69) Survival (median): Oral 33.0 weeks (95%CI, 29.1-42.2; range, 0.3-139.1); iv 35.0 weeks (95%CI, 31.0-37.4; range, 0.77-1.25); hazards ratio=0.98 (95%CI, 0.77-1.25)</td>
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<td>Major adverse effects</td>
<td>Most frequent grade 3/4 toxicities [topotecan arm]: neutropaenia 61%; thrombocytopaenia 38%; anaemia 25%; diarrhoea 6%; toxic deaths 6%.</td>
<td>Proportion and type of serious adverse effects were similar between oral and iv topotecan study arms. Most frequent grade 4 toxicities and</td>
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**Estimated cost and cost impact**

The cost of oral topotecan has yet to be determined. Intravenous topotecan given at 1.5 mg/m$^2$/day for 5 consecutive days costs in the region of £950 to £1,500 based on vial size and assuming wastage$^a$.

**Potential or intended impact – speculative**

**Patients**
- ☐ Reduced morbidity
- ☐ Reduced mortality or increased survival: Increased time to disease progression
- ☐ Improved quality of life for patients and/or carers
- ☐ Quicker or more accurate diagnosis
- ☐ Earlier identification of disease
- ☐ Other:

**Services**
- ☐ Increased use e.g. length of stay, out-patient visits
- ☐ Service reorganisation required
- ☐ Staff or training required
- ☐ Decreased use: Home administration of oral treatment compared with services required for iv therapy
- ☐ Other:

**Costs**
- ☐ Increased unit cost compared to alternative
- ☐ Increased costs: more patients coming for treatment
- ☐ Increased costs: capital investment needed
- ☐ Savings:
- ☐ Other: Unknown

**References**


$^a$ Costs taken from the British National Formulary, Number 52 (September 2006). Assumes an average person has 1.7m$^2$ body surface.

12 GlaxoSmithKline. An open-label, multicentre, randomised, phase III comparator study of oral topotecan versus intravenous topotecan for second-line therapy in patients with SCLC who have relapsed greater than or equal to 90 days after completion of first-line therapy. Study No.: SKF-104864/396. Available at: http://ctr.gsk.co.uk/summary/topotecan/studylist.asp [accessed 29/01/07].