Amrubicin for small cell lung cancer  
– relapsed and/or refractory, extensive disease

September 2008

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Amrubicin for small cell lung cancer – relapsed and/or refractory, extensive disease

Target group
- Small cell lung cancer (SCLC): extensive stage disease – second line, sensitive\(^a/\)relapsed and/or refractory\(^b/\).

Technology description
Amrubicin is an anthracycline anticancer antibiotic that acts as a DNA intercalator in cancer cells via inhibition of DNA topoisomerase-II. Amrubicin is administered at 40mg/m\(^2\) intravenously (IV) for three consecutive days, starting on day 1 of a 21-day cycle for a mean 3-4 cycles.

Innovation and/or advantages
Amrubicin may improve survival with less toxicity than topotecan.

Developer
Celgene Ltd.

Availability, launch or marketing dates, and licensing plans:
Amrubicin has orphan drug status in the EU and USA and is in phase III clinical trials for SCLC.

NHS or Government priority area:
The topic is relevant to the Cancer Reform Strategy (2007) and the NHS Cancer Plan (2000).

Relevant guidance
- NICE technology appraisal in development. Small cell lung cancer (second line) – topotecan. Expected date of issue to be confirmed (17\(^{th}\) wave).
- NICE IP guidance. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for mediastinal masses. 2008\(^2\).
- NICE IP guidance. Percutaneous radiofrequency ablation for primary and secondary lung cancers. 2006\(^3\).
- NICE IP guidance. Photodynamic therapy for localised inoperable endobronchial cancer. 2005\(^4\).
- NICE IP guidance. Cryosurgery for malignant endobronchial obstruction. 2005\(^5\).
- NICE IP guidance. Photodynamic therapy for advanced bronchial carcinoma. 2004\(^6\).
- SIGN. Management of patients with lung cancer. 2005\(^7\).

Clinical need and burden of disease
SCLC is a highly malignant form of bronchogenic carcinoma mostly arising in the central region of the lung, in a main bronchus. SCLC occurs mainly in people with a history of tobacco smoking. Signs and symptoms include chest pain, dyspnea, cough and wheezing. The involvement of adjacent structures can cause hoarseness, dysphagia and superior

\(^a\) Response to first line platinum-based chemotherapy with subsequent progression.
\(^b\) No objective response to prior platinum-based therapy or progression.
vena cava syndrome (obstruction of blood flow through the superior vena cava). Additional symptoms associated with distant metastasis may also be present. In 2005, lung cancer was the second most common cancer in men and third most common cancer in women, accounting for 33,183 new cases in England and Wales. In 2006, there were 29,271 registered deaths in England and Wales.

SCLC constitutes around 20% of all lung cancers, an estimated 6,637 of new cases in England and Wales. Of these, around 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, an estimated 3,982 cases in England and Wales.

SCLC is the most aggressive pulmonary tumour. The initial remission rate with chemotherapy is estimated at 45-75% for those with limited-stage disease, and 20-30% for those with extensive disease. 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.

Existing comparators and treatments
The majority of patients with SCLC present with systemic disease precluding surgery with curative intent. Chemotherapy is the main treatment option for SCLC. The NICE lung cancer clinical guideline advises that:

- All patients with newly diagnosed SCLC should be offered a platinum-based chemotherapy (e.g. cisplatin and etoposide) and multi-drug regimes.
- 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.

Prophylactic cranial irradiation (PCI) may also be considered, as the risk of developing central nervous system metastases within 2 to 3 years after starting treatment is high.

Treatment options for patients with refractory disease are limited to topotecan, which is indicated for the treatment of patients with relapsed SCLC for whom re-treatment with the first-line regimen is not considered appropriate.

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial code, name</th>
<th>NCT00547651: SCLC; amrubicin vs topotecan; phase III.</th>
<th>SCLC; amrubicin vs topotecan; phase II.</th>
<th>SCLC; extensive; refractory or progressive; amrubicin; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Celgene.</td>
<td>-</td>
<td>Celgene.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing</td>
<td>Abstract15</td>
<td>Abstract16</td>
</tr>
<tr>
<td>Participants in trial</td>
<td>n=620; adults; SCLC; extensive or limited; sensitive or refractory; failure after chemotherapy. Randomised to amrubicin</td>
<td>n=75; adults; SCLC; extensive; sensitive to first line chemotherapy. Randomised to amrubicin 40mg/m² IV for 3 days,</td>
<td>n=75; adults; SCLC; extensive; refractory. All patients receive amrubicin 40mg/m² IV for 3 days, starting on day 1 of a 21-day</td>
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<tr>
<td>Follow up</td>
<td>-</td>
<td>Until disease progression or unacceptable toxicity.</td>
<td>Until disease progression or unacceptable toxicity.</td>
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<tr>
<td>Primary outcome</td>
<td>Overall survival (OS).</td>
<td>Response; OS; PFS.</td>
<td>Objective tumour response rate.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Objective response rate (ORR); progression-free survival (PFS); duration of response (DOR) ; time to tumour progression (TTP); safety; quality of life (QOL).</td>
<td>Safety</td>
<td>OS; PFS.</td>
</tr>
<tr>
<td>Key results</td>
<td>-</td>
<td>Statistically significant response rate with amrubicin (16/40 responded). 2 on topotecan had a partial response.</td>
<td>Partial response: 13/39 patients.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Study started Sep 2007. Expected completion March 2011.</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>-</td>
<td>Most commonly reported were haematological and gastrointestinal (GI).</td>
<td>Most commonly reported were GI and haematological.</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Trial code, name</th>
<th>NCT00319969: SCLC; extensive stage; sensitive, recurrent or progressive disease; amrubicin vs topotecan; phase II.</th>
<th>NCT00388960: SCLC; extensive stage; amrubicin vs etoposide-cisplatin; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Celgene</td>
<td>Celgene</td>
</tr>
<tr>
<td>Status</td>
<td>Completed; unpublished results.</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Location</td>
<td>Europe (inc UK).</td>
<td></td>
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<tr>
<td>Design</td>
<td>Randomised, open label, controlled.</td>
<td>Randomised, open label, controlled.</td>
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<tr>
<td>Participants in trial</td>
<td>n=76; adults; SCLC; extensive; sensitive to first line platinum-based chemotherapy; recurrent or progressive disease. Randomised to amrubicin 40mg/m² IV for 3 days, starting on day 1 of a 21-day cycle, or topotecan 1.5 mg/m² for 5 days starting on day 1.</td>
<td>n=81; adults; SCLC; extensive. Randomised to amrubicin alone, or amrubicin with cisplatin vs etoposide with cisplatin.</td>
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<tr>
<td>Primary outcome</td>
<td>Objective tumour response rate.</td>
<td>Objective tumour response rate.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>OS; Time to tumour progression; PFS; toxicity; cardiomyopathy; regression of central nervous system metastases.</td>
<td>OS; PFS; toxicity.</td>
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<tr>
<td>Key results</td>
<td>Amrubicin vs topotecan: Overall response rates were 36% and 8% respectively (p=0.012); median PFS were 130 days and 100 days respectively.</td>
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<tr>
<td>Adverse effects</td>
<td>Generally well tolerated with myelosupression as the main dose-limiting toxicity.</td>
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</table>
Estimated cost and cost impact

The cost of amrubicin has not been determined. Additional costs will be those associated with IV infusion.

Topotecan IV given at 1.5 mg/m²/day for 5 consecutive days costs in the region of £950 to £1,500 based on vial size and assuming wastage.

Potential or intended impact – speculative

Patients

- Reduced morbidity
- Quickened, earlier, or more accurate diagnosis of identification of disease
- Other:
- None identified

Services

- Increased use: e.g. increased length of stay in hospital; outpatient visits
- Decreased use
- Other:
- None identified

Costs

- Increased unit cost compared to alternative
- New costs:
- Other:
- Savings:
- Other: unsure of relative cost

References

8 Orphanet. Lung cancer, small cell. Available at: http://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=10953&Disease_Disease_Search_diseaseGroup=small-cell-lung-cancer&Disease_Disease_Search_diseaseType=Pat&Disease(s)%20concerned=Lung-cancer--small-cell&title=Lung-cancer--small-cell&search=Disease_Search_Simple (accessed 4.9.08)

 Assumes an average person has 1.7m² body surface.


