Manufacturer Submission

To

The National Institute for Health and Clinical Excellence

By

GlaxoSmithKline UK

Multiple technology appraisal of topotecan for the treatment of small cell lung cancer

5 December 2008

Glossary of terms

ASC	Active Symptom Control
AE	Adverse Event
BNF	British National Formulary
BSA	Body Surface Area
BSC	Best Supportive Care
CAV	Cyclophosphamide, Adriamycin [Doxorubicin], Vincristine
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CSR	Clinical Study Report
CT	Computerised Tomography
CTC	Common Toxicity Criteria
CUA	Cost Utility Analysis
DLT	Dose Limiting Toxicities
ECHO	Echocardiogram
ECOG PS	Eastern Co-operative Oncology Group Performance Status
EMEA	European Medicines Evaluation Agency
EQ-5D	EuroQoL questionnaire
FACT-L	Functional Assessment of Cancer Therapy-G and Lung Cancer Subscale
GEE	Generalized Estimating Equations
GI	Gastro Intestinal
GSK	GlaxoSmithKline
HR	Hazard Ratio
ICER	Incremental Cost Effectiveness Ratio
IV	Intravenous
LY	Life Years
ITT	Intent to treat
LYG	Life Years Gained
MAA	Marketing Authorisation Application
MI	Myocardial infarction
MRI	Magnetic Resonance Imaging
MUGA	MUltiple Gated Acquisition scan
NA	Not Applicable
NCI	National Cancer Institute
NE	Not Evaluable
NR	Not Recorded / Reported
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PR	Partial Response
PP	Per Protocol
PS	Performance Status
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumours
RCT	Randomised controlled trial
SAE	Serious Adverse Event
SCLC	Small Cell Lung Cancer
SD	Standard Deviation
SD	Stable Disease (in context of assessing disease progression)
SE	Standard Error
SG	Standard Gamble
SPC	Summary of Product Characteristics
TOI	Trial Outcome Index
TFI	Treatment Free Interval
TTP	Time to Progression

VAS	Visual Analogue Scale
WBC	White Blood Cell(s)
WHO	World Health Organisation

Acknowledgements

GlaxoSmithKline UK would like to thank the following external contributors

- Kleijnen Systematic Reviews Ltd (systematic review)
- Dr Stephen Morris. Brunel University (cost-effectiveness analysis)
- United Biosource Corporation (UBC) (economic model validation)
- Professor Alistair McGuire. London School of Economics (economic model validation)

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1. EXECUTIVE SUMMARY

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Background information

Lung cancer is one of the most common cancers in the UK, accounting for some 15% of all malignancies in males and 11% in females in 2005. There were 33,181 new cases of lung cancer in England and Wales during the same year. [1] Small cell lung cancer (SCLC) is responsible for about 10-15% of all cases of lung cancer (approximately 3,300 – 5,000 cases per year) with non small cell lung cancer (NSCLC) accounting for the remaining 85-90%.[2] SCLC is a very aggressive type of neoplasm which grows rapidly and spreads quickly to distant sites. At the time of diagnosis approximately two thirds of patients with SCLC have extensive disease (defined as tumour with obvious metastatic lesions), with the remaining one third having limited disease (defined as tumour confined to the same hemithorax).[3,4] The prognosis of this condition is poor; the life expectancy of those with untreated SCLC is about 3.5 months for limited disease and 6 weeks for extensive disease.[5]

SCLC is highly chemosensitive, with platinum-based multi-drug therapy (e.g. cisplatin and etoposide) being the usual recommendation for first line chemotherapy. [6] In the context of England and Wales, approximately 58% of newly diagnosed SCLC patients currently receive first line chemotherapy.[7] Whilst response rates of up to 85% are observed,[8] the duration of the response is short and relapse occurs rapidly in virtually all cases.[9] At relapse patients are deemed to have incurable disease, and the goals of further chemotherapy are prolongation of survival, increased time to disease progression and symptom control, whilst maintaining QoL.

Current NICE guidelines for lung cancer recommend that second-line chemotherapy is offered to patients at relapse only if their disease responded to first-line chemotherapy.[10] It is generally accepted that the longer the time to progression (TTP) following first line therapy, the more likely the disease is to respond to a second treatment with cytotoxic therapy [11,12] A recent UK survey indicates that approximately 48% of relapsed SCLC patients would be considered by clinicians as candidates to receive second line chemotherapy.[13]

Second-line therapy consists of either re-treatment with the first-line therapy, or treatment with an alternative therapy. Re-treatment with first line therapy is the standard approach but only a minority of patients have an adequate performance score, a satisfactory recovery from the treatment-specific toxicities, and a sufficiently long time to progression (TTP) following first line chemotherapy to be considered eligible.[14] The majority of patients need alternative therapy, and there is a great need for new, well tolerated regimens for these patients.[15]

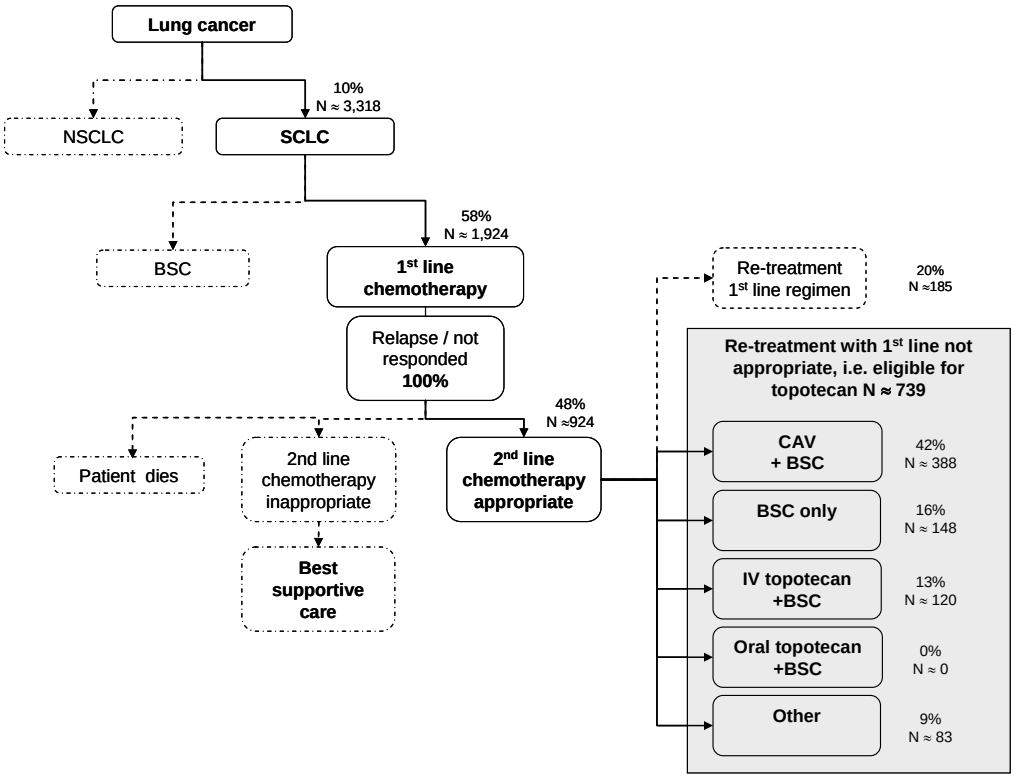
In UK clinical practice relapsed SCLC patients ineligible for re-treatment with first line chemotherapy are usually given an IV anthracycline based regimen, most commonly cyclophosphamide, adriamycin and vincristine (CAV).[14] Before the licensing of topotecan (IV and oral) palliative treatment with best supportive care (BSC) was the main alternative for those patients not considered suitable to receive CAV.

Topotecan: Eligible population and comparators

Topotecan acts by inhibiting topoisomerase I, an enzyme that is required for DNA replication, leading to cell death. It can be administered either intravenously or orally. European marketing authorisation for the SCLC indication was granted in January 1996 and March 2008 for the IV and oral formulations of topotecan respectively. Topotecan is indicated as monotherapy for patients with relapsed SCLC for whom re-treatment with the first-line regimen is not considered appropriate.

The figure below outlines the treatment pathway for SCLC patients in current clinical practice, and defines the place of topotecan within the pathway in terms of eligibility and comparators.

Figure. SCLC – treatment pathway



CAV, IV topotecan, oral topotecan and BSC constitute the key interventions available for the population in which topotecan is licensed. In a minority of patients several other treatments are used in this setting, e.g. vincristine, etoposide and carboplatin monotherapies. Use of these miscellaneous therapies is inconsistent and minimal and, as such, they are not considered as key comparators in this evaluation.

Comparative clinical effectiveness

A systematic review was undertaken to identify the clinical evidence available for topotecan and its comparators in the target patient population, as defined above. Four studies were identified in this setting: one study comparing intravenous topotecan with CAV (von Pawel 1999 – study 090), two studies comparing oral topotecan with intravenous topotecan (von

Pawel 2001-, Eckardt 2007 – studies 065 and 396 respectively), and one study comparing oral topotecan with best supportive care (O'Brien 2006 – study 478). These studies provide the evidence base which allows the following comparisons to be made.

- IV topotecan versus CAV (study 090 - von Pawel 1999[16]) This multicentre randomised trial showed that IV topotecan is at least as effective as CAV in relapsed SCLC patients. No significant differences in the efficacy variables between IV topotecan and CAV were observed: response rate (24.3% versus 18.3%; p=0.285), TTP (median, 13.3 versus 12.3 weeks; p=0.552), or overall survival (median, 25.0 versus 24.7 weeks; p=0.795) However, several disease-related symptoms improved to a significantly greater extent with topotecan than with CAV (dyspnoea p=0.02, fatigue p=0.032, anorexia p=0.042, hoarseness p=0.043, and interference with daily activity p=0.023).[16]

- IV topotecan versus oral topotecan (study 396 - Eckardt 2007[17]; study 065 - von Pawel 2001[18]) The two head to head phase III (396) and phase II (065) randomised trials evaluating the two topotecan formulations showed no significant differences in overall survival, QoL, individual symptom scores, median time to progression and median duration of response between IV and oral topotecan.[17,18]

- Oral topotecan versus CAV Although there has been no clinical trial to evaluate these two interventions, based on the above clinical evidence it is reasonable to assume that oral topotecan is at least as effective as CAV in terms of clinical outcomes, with added improved symptom control, and the convenience of oral home administration.

- Oral topotecan plus BSC versus BSC alone (study 478 – O'Brien 2006[19]) This recent multicentre randomised trial evaluated the role of oral topotecan + BSC versus BSC alone in 141 patients with relapsed SCLC who were not considered as candidates for standard IV therapy (study 478). This was a unique trial in the context of SCLC in which a BSC control group was used while evaluating survival, response and symptoms. BSC is considered as a valid comparator as in the UK it is currently the management option of choice in the majority of relapsed SCLC patients who are not considered suitable to receive IV treatment with CAV.

A clinically and statistically significant improvement in the primary endpoint of overall survival was observed in the oral topotecan arm (p=0.01). The unadjusted hazard ratio for oral topotecan relative to BSC was 0.64 (95% CI, 0.45– 0.90), indicating a 36% lower risk for death in the oral topotecan group. The median survival time was 86% longer in the topotecan arm than in the BSC arm (25.9 weeks versus 13.9 weeks). The 6-month survival rates were 49% in the topotecan arm and 26% in the BSC arm. Quality of life (measured with EQ-5D questionnaire) deteriorated significantly faster in patients receiving BSC alone.[19]

Subgroup analyses showed that prolongation of survival in the topotecan group was preserved when analysed according to different patient characteristics defined at baseline: sex, TTP from prior therapy (≤ 60 days or >60 days), performance status (PS) (0/1 or 2), and presence of liver metastases. Further extrapolation of these findings should be viewed with caution due to the small subset of patients and the proclivity for subgroup analysis to detect spurious effects.

Cost-effectiveness of topotecan

CAV, IV topotecan, oral topotecan and BSC constitute the key available interventions for patients with relapsed SCLC who can tolerate further chemotherapy and for whom re-treatment with the first-line regimen is not considered appropriate. In the majority of cases patients are given an IV anthracycline based regimen, most commonly CAV (see figure 1). Cost-effectiveness comparisons between topotecan and CAV have not been undertaken as it is recognised that topotecan (IV and oral) would not provide cost effective alternatives to CAV in the majority of patients given their relatively higher acquisition costs.

Discussions with clinical experts highlight a subset of patients for whom CAV would not be appropriate, but who may be suitable for chemotherapy with topotecan (IV and oral). These are patients who have contraindications to components of the CAV regimen. Patients' ineligibility for CAV include those with serious pre-existing cardiovascular problems as well as patients with pre-existing neuropathy (from prior cisplatin treatment or concurrent disease), which may be exacerbated by the neurotoxic effect of vincristine.

When compared with oral topotecan the IV formulation has a similar efficacy profile but is associated with higher acquisition and administration costs. Thus, it is unlikely to be a cost effective alternative to oral topotecan, which would be the logical choice in this setting. Another subset of patients suitable for treatment with oral topotecan may include relapsed SCLC patients for whom IV therapy access is difficult or refused.

For these subsets of patients not considered as candidates for standard intravenous therapy treatment with CAV or IV topotecan would not be considered an option; and currently their only available options are oral topotecan and BSC alone. Therefore the cost-effectiveness and NHS impact sections of this submission focus on an evaluation of oral topotecan added to BSC relative to BSC alone.

Relative to BSC alone, oral topotecan added to BSC is a cost effective therapy in patients with relapsed SCLC not considered as candidates for standard intravenous therapy. The baseline estimate of the incremental cost per QALY gained was £26,833. According to NICE methodological guidance, [20] for an intervention with an incremental cost per QALY gained in the £20,000-£30,000 range to be judged acceptable for use in the NHS depends on the degree of uncertainty around the ICER, whether or not the change in HRQOL was adequately captured, and the innovative nature of the technology, specifically if the innovation adds substantial benefits which are not adequately captured by QALYs.

A range of deterministic sensitivity analyses suggests that cost-effectiveness ratios are in the range £22,512-£40,253/QALY, and at a cost-effectiveness threshold of £30,000 oral topotecan+BSC would be cost-effective relative to BSC alone in 60% of cases. The main drivers of uncertainty were measurement of HRQOL, drug administration cost and the cost of treating adverse events.

A strength of this evaluation is that it is based on patient level HRQOL data from the same sample of patients used to measure survival and costs. However, it should be noted that valuations of health states have been obtained from the general UK population without reference to the disease context. There is an argument that patients (and perhaps the general public) place a higher value on a QALY gained from prolonged survival towards the end of a life that is being 'cut short' than a QALY gained elsewhere (such as a small increase in quality of life over a long period of time). Recent research also suggests that the UK public applies greater priority to diseases with greater severity and hence that in these patients a higher threshold or 'QALY weighting' should be considered.[21] Therefore, the full benefit to patients and their carers/dependants of oral topotecan+BSC may not be fully represented in the cost/QALY estimates. We also suggest that this is viewed in the light of the ongoing NICE consultation document on end of life medicines. Topotecan is indicated for a very small population (fewer than 1,000 patients) with limited life expectancy of a few months, even when treated. Topotecan has been shown to almost double overall survival to six months when added to BSC, an extension to life which is extremely valuable to patients and their families faced with such a poor prognosis.

Oral topotecan is the first and only therapy licensed and proven for use specifically in patients with relapsed SCLC for whom re-treatment with the first-line regimen is not considered appropriate. An oral formulation makes it possible for treatment to be self administered which results in minimal disruption to daily life and limited capacity/resource implications for the NHS. Therefore oral chemotherapy constitutes a convenient alternative for patients who otherwise would receive only best supportive care.

Several subgroups of patients were examined based on pre-specified and post hoc subgroup analyses. The results are suggestive of increased cost effectiveness in several subgroups of patients (e.g. those without liver metastases and patients who relapse after an off-therapy period of at least 90 days). Whilst interesting, these analyses should be viewed with appropriate caution.

Resource implications for the NHS

Oral topotecan could be implemented in England and Wales at an initial cost to the NHS in year one of approximately £840,000, for patients who are considered unsuitable for IV chemotherapy. This assumes a 100% uptake in the eligible population, and acquisition costs as well as resource use costs involved in the administration of topotecan in these patients.

Conclusions

Oral topotecan provides a clinically and cost-effective treatment in patients with relapsed SCLC who are not considered as candidates for standard intravenous therapy with CAV, and for whom best supportive care is currently the only option. We therefore ask NICE to recommend its use in this specific group of patients who otherwise have very limited treatment options in the last stages of their disease.

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