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Health Technology Appraisal

Topotecan for the second-line treatment of small cell lung cancer

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Introduction:

Small cell lung cancer (SCLC) accounts for between 10 and 20% of lung cancers diagnosed within England and Wales (i.e. 3300 – 6600 new cases per year). It is considered to be an aggressive form of lung cancer that grows rapidly and has frequently spread to distant sites at the time of diagnosis.

Initial treatment usually consists of platinum (either cisplatin or carboplatin) and etoposide based combination chemotherapy with response rates of 60 – 80% (Pujol et al 2000). Treatment with radiotherapy may be used to consolidate response. Despite high initial response rates, most patients will relapse. It is estimated that approximately 50% of patients who relapse will be considered for second line chemotherapy. Depending upon the duration of response to the first line schedule, the choice of second line chemotherapy may be either re-challenge with platinum and etoposide (usually considered if progression free survival > 6 months) or consideration for an alternative anthracycline based chemotherapy regime such as CAV (cyclophosphamide, doxorubicin and vincristine). Both schedules are intra venous and administered every 3 weeks, usually as an out-patient.

Evidence for Topotecan:

Topotecan, a topoisomerase I inhibitor is licensed as a monotherapy for patients with relapsed small cell lung cancer for whom re-treatment with the first line regime is not appropriate. It is available as both oral and intra-venous preparations.

Randomised clinical trials have demonstrated equivalent clinical efficacy for oral and intra-venous topotecan (von Pawel et al 2001, Eckardt et al 2007). A single randomised trial has compared intra-venous topotecan with the current UK standard second line treatment CAV. This study found similar response rates (24% topotecan versus 18% CAV), time to progression (13 versus 12 weeks) and overall survival (25 versus 24.7 weeks) (von Pawel et al 1999). There is no direct head to head comparison between oral topotecan and CAV.

A further trial compared oral topotecan with best supportive care (BSC) for patients not considered suitable for second line intra-venous chemotherapy (O'Brien et al 2006). This study showed a significant improvement in median survival from 13.9 weeks for BSC to 25.9 weeks for topotecan. Whilst the two study groups were well matched, a high proportion of patients had a good performance status (70% WHO performance status 0 or 1), had a relatively young age (mean 59 years) and a quarter of patients had been treated with surgery as part of their treatment. It is not clear to what extent this patient population is representative of usual UK practice or exactly how patients were selected for this study. It is likely in many UK centres that this patient group, outside of a clinical trial, would have been considered for CAV.

Overall my conclusions from the clinical evidence are:

1. Oral and intra-venous topotecan demonstrate equivalent clinical activity and similar toxicity.
2. Topotecan is equivalent to CAV as second line chemotherapy for relapsed SCLC.

Considerations for Topotecan

My assessment of the evidence in support of this appraisal is as follows:

1. Intra-venous (iv) topotecan demonstrates equivalent activity to the standard UK second line chemotherapy CAV when re-challenge with a platinum/etoposide schedule is not appropriate. There is no clear advantage for iv topotecan over CAV in terms of schedule, toxicity or efficacy.
2. Extrapolation of the evidence implies equivalent efficacy for oral topotecan to iv and as such to CAV. Again there is no clear advantage in terms of toxicity.
3. Approval of oral topotecan compared to the standard iv treatment CAV could offer advantages to patients in terms of a more convenient treatment schedule. This is particularly important for patients with relapsed SCLC where prognosis is poor. For the NHS it would mean fewer patients attending chemotherapy day units for iv therapy and fewer out-patient attendances. This and the cost of making up intra-venous chemotherapy must be considered in the economic analysis.
4. There is no clear evidence that for all patients with relapsed SCLC, approval of oral topotecan would allow treatment of a much wider group of patients ie that it could replace BSC and therefore improve survival for a group of patients not otherwise considered fit for chemotherapy.
5. Whilst intra-venous chemotherapy with CAV remains a standard second line treatment, there will be a limited number of patients for whom it would not be appropriate (eg those with significant cardiac co-morbidity, peripheral neuropathy). In this group of patients, approval of oral topotecan would offer the option of an effective second line treatment with significant benefit compared to best supportive care.