Scottish Medicines Consortium

Re-Submission

erlotinib, 100 and 150mg film-coated tablets (Tarceva®) No. 220/05
Roche

5 May 2006

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 re-submission

Erlotinib (Tarceva®) is accepted for restricted use within NHS Scotland for the treatment of patients with locally advanced or metastatic non-small cell lung cancer, after failure of at least one prior chemotherapy regimen. When prescribing erlotinib, factors associated with prolonged survival should be taken into account. No survival benefit or other clinically relevant effect of the treatment have been demonstrated in patients with epidermal growth factor receptor (EGFR)-negative tumours.

Erlotinib is restricted to use in patients who would otherwise be eligible for treatment with docetaxel monotherapy. No economic case has been made for those whose performance status would make them ineligible to receive docetaxel.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

erlotinib 100 and 150mg film-coated tablets (Tarceva®)

Indication

For the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen. When prescribing erlotinib, factors associated with prolonged survival should be taken into account. No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with epidermal growth factor receptor (EGFR)- negative tumours.

Dosing information

150mg daily, adjusted by reducing in 50mg steps, if necessary.

UK launch date

September 2005

Comparator medications

Other second-line treatment options are docetaxel monotherapy, pemetrexed, best supportive care.

Cost of relevant comparators

Drug	Dose	Cost of a 21 day treatment cycle	Cost of 4 cycles of treatment
Erlotinib	**150mg daily**	**£1142**	**£4568***
Docetaxel	75mg/m^2 on day one of a 21 day cycle	£860- £1023	£3440 - £4092
Pemetrexed	500mg/m^2 on day one of a 21 day cycle	£1600	£6400

Costs for docetaxel and pemetrexed are based on prices in the BNF no. 50 and on body surface areas of 1.6m^2 to 1.8m^2. *Erlotinib is given continuously and not in cycles. The cost quoted equates to 84 days treatment and is based on NHS prices accessed on evadis on 13th March 2006.

Summary of evidence on comparative efficacy

The EGFR is a member of the ErbB family of transmembrane tyrosine kinase receptors which includes ErbB1 (HER1 and EGFR). The expression of EGFR is common in a number of normal epithelial tissues but is elevated in several solid tumours including a high proportion of NSCLCs. Erlotinib is a potent, orally active inhibitor of the HER1/EGFR tyrosine kinase. It reduces EGFR autophosphorylation in intact tumour cells by competing with adenosine triphosphate for the phosphate binding site of the tyrosine kinase, thus inhibiting the triggering of the biochemical cascade.

In the pivotal, double blind, phase lll study, 731 patients with incurable Stage IIIB/IV NSCLC who had already received at least one, but not more than two, prior lines of chemotherapy and had Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 – 3, were randomised on a 2:1 basis to receive erlotinib 150mg daily or placebo, until disease

progression or unacceptable toxicity. There was no pre-selection of patients based on EGFR expression or performance status (66.5% of patients had a PS of 0-1 and 33.5% a PS of 2-3). All study patients received active supportive care. The primary outcome measure was overall survival with secondary end-points of progression free survival (PFS), response rates using the Response Evaluation Criteria in Solid Tumours (RECIST), response duration, adverse event profile according to the Common Toxicity Criteria of the National Cancer Institute and quality of life (QoL) as measured by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the lung cancer module QLQ-LC13. Analysis of the study was event-driven with 587 deaths having occurred at the time of analysis (378 erlotinib and 209 placebo patients). Of the remaining patients, 110 in the erlotinib group and 34 in the placebo group were still alive, with 7 patients lost to follow-up. Erlotinib increased median overall survival from 4.7 months (95% CI, 4.1-6.3) in the placebo arm to 6.7 months (95% CI, 5.5-7.8) in the erlotinib arm, a 43% relative improvement with an adjusted hazard ratio (HR) in the erlotinib group relative to placebo of 0.73 (95% CI, 0.60-0.87, p<0.001). The HR and p value were adjusted for stratification factors at randomisation and EGFR expression status. The percentage of patients surviving at 12 months was 31% and 22%, respectively. Median PFS increased from 8 weeks (95% CI, 8.43-12.43) for placebo to 9.7 weeks (95% CI 7.86-8.14) for erlotinib, adjusted HR, 0.61 (95% CI, 0.51-0.74; p<0.001). At the time of analysis, 682 patients had progressed (450 in the erlotinib group and 232 in the placebo group). In the 427 patients receiving erlotinib who had measurable disease, the overall response rate was 8.9% (95%CI, 6.4-12.0); 38 patients had a complete (n=4) or partial response; 150 (35%) had stable disease and 164 (38%) had progressive disease. For the 211 patients in the placebo group the response rate was 0.9% (95% CI, 0.1-3.4); two patients had a complete (n=1) or partial response, 56 (26%) had stable disease and 121 (57%) had progressive disease. The median duration of response in the erlotinib group was 34.2 weeks and ranged from 9.7 weeks to 58+ weeks.

The primary endpoint for the QoL analyses was defined as the time to deterioration of cough, dyspnoea and pain. Deterioration was specified as a change from baseline of 10 points or more on a 100-point scale. Deterioration of cough was reported in 32% vs 41% of patients, deterioration of dyspnoea by 40% vs 44%, worsening fatigue by 51% vs 55% and worsening pain by 43% vs 51% of patients in the erlotinib and placebo arm, respectively. Patients in the erlotinib arm had significantly longer time to deterioration for these three tumour-related symptoms: 4.9 vs 3.7 months for cough (p=0.04), 4.7 vs 2.9 months for dyspnoea (p=0.03), and 2.8 vs 1.9 months for pain (p=0.04). In addition to QoL benefits observed for these tumour-related symptoms, differences were also seen in the physical function domain (31% improved on erlotinib vs 19% on placebo, p=0.01) and in global QoL (35% vs 26%, p<0.01). The European Public Assessment Report (EPAR) confirmed that treatment with erlotinib resulted in symptom benefits by significantly prolonging time to deterioration in cough, dyspnoea and pain compared with placebo, but that a general improvement of QoL could not be concluded from the data.

Summary of evidence on comparative safety

In the pivotal study, erlotinib was associated with a similar level of reported adverse events as placebo (99% vs 96% for erlotinib vs placebo). However, more patients in the erlotinib arm experienced treatment-related serious adverse events than in the placebo arm (8% vs 3%). Two deaths in the erlotinib arm were attributed to toxicity from protocol treatment and two to a combination of NSCLC and protocol treatment complications. It was noted in the EPAR that an increase in treatment-related deaths had not been observed in previous studies of single treatment with erlotinib compared with placebo. Rash in 75% of patients and diarrhoea in 54% were the most common adverse effects but were generally mild to moderate in intensity; only 9% of patients experienced a rash ≥ grade 3, resulting in 12% requiring dose reductions and 14% having their treatment interrupted. The aetiology of the

rash is unknown, but it superficially resembles acne and is usually seen on the face and trunk and can range from mild skin reddening to a quite florid rash which can become infected. Diarrhoea was seldom severe and generally responded well to treatment with standard antidiarrhoeal medications. Other adverse effects occurring at least twice as often with erlotinib as with placebo were pneumonia, dehydration, vomiting and fatigue.

Erlotinib is metabolised in the liver primarily by CYP3A4 and is a moderate inhibitor of CYP3A4 and CYP2C8. Concomitant use of CYP3A4 substrates and modulators may require some caution and dose adjustment.

Summary of clinical effectiveness issues

There are two main clinical effectiveness issues: the comparator used in the pivotal trial and the selection of patients who would best benefit from this treatment. At present, there are two other drugs licensed for this indication, pemetrexed and docetaxel. The company chose to compare erlotinib against active supportive care to include patients of all performance status who might benefit from erlotinib. However, only 9% of patients in the trial had a performance status of 3, with the remaining 90% having performance status of 0-2. Unfortunately, it is therefore only possible to make indirect comparison of efficacy and safety with docetaxel, currently the only treatment recommended as second line treatment in NSCLC after failure of prior chemotherapy by the SIGN guideline on the management of lung cancer (February 2005). However, the regulatory authorities have concluded that due to the observed overall survival it is unlikely that erlotinib is inferior to single agent docetaxel or pemetrexed in this group of patients.

Identifying and pre-selecting the patients most likely to respond to HER1/EGFR- targeted agents is important in using these agents cost effectively. Patients with EGFR negative status did not obtain a significant survival benefit with erlotinib as indicated by a 0.93 hazard ratio in this subgroup This issue was referred to the scientific advisory group (SAG) of the European Medicines Agency (EMEA) who concluded that there is no pharmacological reason for using erlotinib in EGFR negative patients, there was no data or rationale to support the existence of a clinically meaningful effect in EFGR negative patients and that EGFR status should be known and taken into account together with all factors associated with response to treatment in order to allow a rational choice of treatment. Subgroup analysis, which was not statistically powered, was suggestive of some patient characteristics providing a better response to treatment with erlotinib. However, the evidence for a reliable predictor of response is at present not available to allow for confident pre-selection of patients. There are a growing number of HER/EGFR compounds which offer benefit to some patients but for which a reliable predictor of response is required both to establish their positive benefit and to enable them to be used cost effectively.

Indirect comparison of the key studies would suggest that erlotinib offers an oral preparation with comparable overall survival outcomes and a more favourable adverse effect profile than docetaxel. When prescribing erlotinib the factors associated with prolonged survival, as suggested by the subgroup analysis, should be taken into account. Approximately 90% of lung cancer cases in Scotland are attributed to tobacco use. In the trial presented, current and ex-smokers had poorer response to erlotinib therapy than non-smokers.

Summary of comparative health economic evidence

A cost utility analysis was presented by the manufacturer comparing erlotinib with docetaxel for the treatment of patients with metastatic non-small cell lung cancer. The main data sources are the pivotal clinical trial for erlotinib arm and another trial for the docetaxel arm of the evaluation. An indirect comparison is made using these data sources as no direct comparison is currently available between erlotinib and docetaxel. The analysis predicts that while there will be additional costs associated with erlotinib, there will also be an increase in the number of QALYs compared to docetaxel. The manufacturer estimates that the net cost per QALY gained will be £4,800 compared to using docetaxel.

In terms of the design of the economic study, the main strengths are that the comparator was appropriate for the group of patients considered in the analysis and an appropriate time horizon was used. However, the group of patients who would not be suitable to receive docetaxel have not been compared to the appropriate comparator. In the clinical evidence section, the key strengths are that utility values were calculated appropriately and that QALYs have been calculated.

The weakness in the handling of resource use and costs is that the duration of treatment in the docetaxel phase III trial equates to 4-5 cycles of docetaxel but experts suggest this might be greater than is standard practice in Scotland. The results produce a cost/QALY that is relatively low in the base case scenario. However, when the number of cycles of docetaxel is lowered to 4, the cost/QALY rises to £22,500.

Currently, patients can be divided into those who are treated with docetaxel and those who are not. With respect to the latter group, no economic data have been presented and hence the case has not been demonstrated.

Patient and public involvement

Patient Interest Group Submission: Roy Castle Lung Cancer Foundation.

Budget impact

The manufacturer estimated budget impact of erlotinib at £221,000 in year 1, rising to £719,000 in year 5.

It is assumed that 122 patients will be switched to erlotinib in year 1, rising to 395 in year 5. These figures are based on the number of patients currently receiving docetaxel. The budget impact would be greater if erlotinib is used in patients with poor performance status who are unfit for docetaxel, though the economic case has not been made in this patient group.

Guidelines and protocols

The Scottish Intercollegiate Guidelines Network. (SIGN) 2005 Guideline 80. Management of patients with lung cancer recommends that in patients with advanced NSCLC the number of chemotherapy cycles should not exceed four and recommended second line therapy for patients with stage IIIB/IV NSCLC and good performance status is docetaxel. The National Institute for Health and Clinical Excellence. (NICE) Clinical Guideline 24. Lung Cancer: The

diagnosis and treatment of lung cancer. February 2005 recommends that docetaxel monotherapy should be considered for use if second line treatment is appropriate for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy.

Additional information

National Institute for Health and Clinical Excellence. (NICE) has a Single Technology Appraisal in development for Erlotinib for the treatment of non-small cell lung cancer. Expected date of issue late 2006.

Erlotinib was reviewed by SMC in 2005 when it was not recommended for use within NHS Scotland for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. The economic case was not demonstrated.

Pemetrexed was reviewed by SMC in April 2006 when in the absence of a submission from the holder of the marketing authorisation, it was not recommended for use within NHS Scotland, as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

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 18 May 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration.

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

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