Scottish Medicines Consortium

pemetrexed, 500mg, powder for reconstitution (Alimta®) No. (342/07)

Eli Lilly

12 January 2007

The Scottish Medicines Consortium has completed its assessment of the above product and advises the NHS Boards and Area Drug and Therapeutic Committees on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

pemetrexed (Alimta®) is not recommended for use within NHS Scotland as a monotherapy for second-line treatment of patients with locally advanced or metastatic non-small cell lung cancer.

Pemetrexed appears to have comparable efficacy and possibly a more favourable toxicity profile compared to another agent used in second–line treatment of non-small cell lung cancer.

However, the economic case has not been demonstrated.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Pemetrexed is indicated as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

Dosing information

The recommended dose of pemetrexed is 500mg/m^2 BSA administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

Product availability date

20th September 2004

Summary of evidence on comparative efficacy

Pemetrexed is a multi-targeted anti-cancer anti-folate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication. Its primary mechanism of action is to inhibit the enzyme thymidylate synthase, resulting in decreased thymidine necessary for pyrimidine synthesis. Pemetrexed also inhibits dihydrofolate reductase and glycinamide ribonucleotide formyl transferase, the latter a folate-dependent enzyme involved in purine synthesis.

A randomised, phase III trial compared the efficacy and toxicity of pemetrexed and docetaxel in patients with advanced non-small-cell lung cancer (NSCLC) previously treated with chemotherapy. Patients were aged ≥ 18 years with histological or cytological confirmation of NSCLC with locally advanced or metastatic disease (stage III or IV) not amenable to curative therapy. Patients had to have received prior chemotherapy, have adequate organ function, an Eastern Cooperative Oncology Group performance status (PS) of 0 to 2 and an estimated life expectancy of at least 8 weeks.

Patients received either 500mg/m^2 pemetrexed as a 10 minute intravenous infusion or 75 mg/m^2 docetaxel as a 1 hour intravenous infusion on day 1 of a 21-day cycle which was repeated until disease progression, unacceptable toxicity or until the patient or the investigator requested therapy discontinuation. Pemetrexed patients also received folic acid 350-1000µg orally daily and vitamin B_{12} injection intramuscularly every nine weeks to reduce toxicities, starting 1-2 weeks before treatment commenced. Both pemetrexed and docetaxel patients received dexamethasone the day before, the day of and the day after treatment (4mg twice daily in the pemetrexed arm as prophylaxis against skin rash and 8mg twice daily in the docetaxel arm to reduce the severity of fluid retention and hypersensitivity reactions).

The primary objective of the study was to compare overall survival between the two treatment groups on an intention-to–treat (ITT) basis. Secondary objectives were to compare toxicities (including use of concomitant supportive measures), objective response rates (RR), progression free survival (PFS), time to progressive disease (TPD), time to treatment failure (TTF), time to response, duration of response, and quality-of-life measurements using the Lung Cancer Symptom Scale (LCSC).

In the primary efficacy analysis the hazard ratio (HR) for overall survival comparing pemetrexed with docetaxel was estimated using the Cox proportional hazards model with treatment as the only co-factor. Non-inferiority would be concluded if the upper bound of the 95% confidence intervals (CI) for this HR was <1.11.

A percent retention analysis was also prospectively planned as a secondary analysis of the primary endpoint, to investigate the hypothesis that pemetrexed retained ≥ 50% of the historical survival benefit of docetaxel over best supportive care (BSC) in an indirect comparison based on a trial comparing docetaxel with BSC. Non-inferiority was defined as HR < 1.21.

An ancillary analysis using Cox multiple regression (CMR) was also planned to identify additional factors that affected survival and to estimate the treatment effect after adjusting for these factors.

A total of 571 patients, were included in the survival analysis; 283 in the pemetrexed arm and 288 in the docetaxel arm. The median survival time for pemetrexed was 8.3 months versus 7.9 months for docetaxel (HR, 0.99; 95% CI, 0.82 to 1.2; non-inferiority p=0.226). Using the percent retention method, the estimate of the percentage of survival benefit (of docetaxel over BSC) retained by pemetrexed was 102% with the lower 95% CI bound of 52%; this was statistically significant (p=0.047, 95% CI 52-157%).

CMR analysis was performed on 532 patients and showed that factors significantly associated with increased survival were PS 0 or 1, stage III disease and time since last chemotherapy. After adjusting for each of those factors, similar survival was seen between treatment groups (HR, 0.93; 95% CI 0.76-1.13; non-inferiority p=0.051).

There were no significant differences in overall RR, (9.1% v 8.8%), PFS, and TPD. Reporting of statistical significance for TTF was ambiguous. Text in the pivotal paper stated that there was no significant difference, although tabulated data showed that TTF was significantly longer in pemetrexed-treated patients than in docetaxel-treated patients (p=0.046). There were also no significant differences in median time to response, median duration of response or median duration of clinical benefit.

Summary of evidence on comparative safety

When compared to docetaxel, patients receiving pemetrexed had lower incidence of Grade 3/4 neutropenia (5.3% versus 40.2%, p<0.001) and febrile neutropenia (1.9% versus 12.7%, p<0.001). Hospitalisations for neutropenic fever were significantly less common with pemetrexed than docetaxel with a total duration of 29 days and 195 days respectively. In addition the percentage of patients receiving granulocyte colony-stimulating factors (G-CSFs) was 2.6% in the pemetrexed arm and 19.2% in the docetaxel arm, p<0.001.

Compared to docetaxel, fewer patients received erythropoietin with pemetrexed (6.8% versus 10.1%, p=0.169) but more patients received RBC transfusions on pemetrexed (16.6% versus 11.6%, p=0.1078).

The incidence of alopecia (all grades) was lower with pemetrexed than docetaxel (6.4% versus 37.7%, p<0.001). Diarrhoea grade 3/4 was also lower with pemetrexed (0.4% versus 2.5%, p=0.069). However, although not statistically significant, the incidence of nausea (30.9% versus 16.7%) and vomiting (16.2% versus 12.0%) was greater with pemetrexed than docetaxel. There was also a greater incidence of rise in alanine transaminase with pemetrexed (7.9% versus 1.4%) than with docetaxel, p<0.028.

Patients on pemetrexed had more hospitalisation days than patients on docetaxel, particularly for non-drug-related and social reasons (1105 versus 650), although patients on pemetrexed had fewer hospital admissions (337 versus 364).

Summary of clinical effectiveness issues

In the analysis of the primary endpoint, the criteria for non-inferiority in overall survival were not met. In the percent retention analysis of overall survival, non inferiority was established for less stringent criteria (HR<1.21, p=0.047), since at least 52% (lower 95% CI) of the survival benefit of docetaxel over BSC was retained by pemetrexed. The scientific discussion of the European Public Assessment Report (EPAR) states that the non-inferiority margin in the primary (fixed margin) analysis would correspond to a more stringent 78% retention of such an effect. However, it notes that this estimate only refers to the sub-group that received 75mg/m^2 and not 100mg/m^2 of docetaxel and does not consider active comparators, weakening the relevance of the proposed non–inferiority margin.

G-CSFs are not used routinely for prophylaxis in Scotland. However, in the pivotal trial only four docetaxel patients and one pemetrexed patient received G-CSF as prophylaxis without a prior event of neutropaenia.

The EPAR comments that the observed upper confidence limits for survival analysis between 1.13 (adjusted) and 1.20 (unadjusted) correspond to pemetrexed retaining 52% to 73% of docetaxel's benefit over BSC and that this corresponds to at most a 3.6 to 16.1 days difference in median survival from the protocol-defined 10% margin, suggesting similarities between treatments.

Summary of comparative health economic evidence

The main analysis presented a Markov model that estimated the cost utility of pemetrexed relative to docetaxel. Docetaxel was the appropriate principal comparator. This was implemented through 21 day cycles over a three year time horizon. Treatment and its immediate effects occurred during the first six cycles, with patients responding, remaining stable, progressing or dropping out of treatment. Treatments were also differentiated by their adverse event rates. After treatment patients could either remain in their current state, move into progressive disease, or die from any of the three disease states.

The clinical effectiveness of pemetrexed was estimated from the pemetrexed arm of the pivotal head to head trial with docetaxel. The clinical effectiveness of docetaxel was estimated from a pooled analysis of the docetaxel arm of the pivotal head to head trial with pemetrexed, coupled with the docetaxel arms of five other studies that had been drawn from the literature.

In terms of clinical effectiveness, this resulted in pemetrexed being superior to docetaxel in all the main transition probabilities of the model such as response rates and likelihood of having progressive disease. Pemetrexed was also estimated as being superior to docetaxel in terms of having lower likelihoods of the main adverse events during treatment.

Quality of life for the various health states within the modelling was estimated through a utility elicitation exercise among 100 members of the general public. The values resulting from this exercise were reasonable.

The overall cost effectiveness was estimated as £18,672 per QALY relative to docetaxel. This was based on an average survival gain of 0.19 years from pemetrexed compared to docetaxel. When quality of life values were factored into this the average gain per patient from pemetrexed was estimated as 0.07 QALYs. The net drug acquisition cost of pemetrexed compared to docetaxel was £1,854 but savings on other health care costs reduced the overall net cost of pemetrexed to £1375.

The main weakness within the modelling was the anticipated additional survival from pemetrexed of 0.19 years; an additional 25% lifespan relative to docetaxel. This gain was not reflected within the clinical effectiveness section of the submission, the pivotal head to head trial of pemetrexed to docetaxel showing no overall survival gain from pemetrexed.

The manufacturer presented an additional analysis with the clinical effectiveness estimates for both docetaxel and pemetrexed being drawn from the pivotal head to head trial. This resulted in a slightly reduced anticipated survival gain from pemetrexed of 0.14 life years, and a higher cost effectiveness ratio of around £53,000 per QALY. However, the anticipation of a survival benefit from modelling based upon the pivotal trial when no such benefit occurred within the trial raised questions as to the validity of the modelling exercise.

The main patient benefits within the modelling seemed to arise from the anticipated increase in life expectancy. This did not reflect the results of the principal head to head clinical trial. As a consequence the cost effectiveness of pemetrexed has not been demonstrated.

Summary of patient and public involvement

Patient Interest Group Submission: Roy Castle Lung Foundation

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) guidelines on the Management of Patients with Lung Cancer- A National Clinical Guideline, No. 80, published February 2005. A review of this guideline will be considered three years from this date.

The National Institute for Health and Clinical Excellence (NICE) guidelines on the Diagnosis and Treatment of Lung Cancer - Guideline No. 24, published February 2005. Expected review date is February 2009.

NICE is currently in progress with a single technology appraisal for pemetrexed: Lung cancer (non- small cell) -pemetrexed. Pemetrexed, for the treatment of non-small cell lung cancer. Expected December 2006.

Additional information: previous SMC advice

Following a re-submission, in May 2006, the SMC advised that erlotinib 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 effects 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.

Additional information: comparators

SIGN advises that second line chemotherapy with docetaxel 75mg/m2 (three weekly) should be considered for stage IIIB/IV NSCLC patients with good performance status.

NICE advises that docetaxel as monotherapy should be considered if second-line treatment is appropriate for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy.

Erlotinib is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. However no survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR-negative tumours.

Additional information: costs

Drug	Body Surface Area (m^2)	Regimen	Cost per 21 day cycle (£)
Pemetrexed powder for reconstitution	**1.8**	**500mg/m^2 by intravenous infusion repeated every 21 days (500 x1.8 =900mg/dose)**	**1,600 (2 x 500mg vials per dose)**
Docetaxel Concentrate for dilution	1.8	75mg/m^2 by intravenous infusion repeated every 21 days (75 x 1.8 = 135mg/dose)	1,023 (1 x 2ml (80mg) vial + 3 x 0.5ml (20mg) vial per dose)
Erlotinib tablets	N/A	150mg orally daily	1142.07

NB 1. Costs for additional vitamin supplements have not been included for pemetrexed.

Additional information: budget impact

Based upon an annual incidence of around 3,800 NSCLC cases of whom 25% will progress to 1st line chemotherapy and of whom 25% will in turn progress to 2nd line chemotherapy, the manufacturer estimated that around 240 patients will be eligible for pemetrexed. Given a market penetration of 5% in year 1 rising to 40% in year 5, the manufacturer estimated that this translates to a gross drug treatment of £54,400 in year 1 rising to £457,000 in year 5. The net drug cost is estimated as £22,000 in year 1, rising to £185,000 by year 5.

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 13 December 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

Hanna N, Shepherd FA, Fossella V, Pereira JR, DeMarinis F, von Pawel J, et al (2004). Randomised phase III trial of pemetrexed versus docetaxel in patients with non-small cell lung cancer previously treated with chemotherapy. J Clin Oncol, 22 (9) 1589-97.

Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al (2000). Prospective randomised trial of docetaxel versus best supportive care in patients with non-small cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol, 18 (10) 2095-103.

Shepherd FA, Rodrigues Pereria J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al (2005). National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med, 14: (353) 2, 123-32.