Clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation

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Scientific summary

First-line chemotherapy for locally advanced or metastatic non-small cell lung cancer

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Scientific summary

Background

Lung cancer is the most common cancer in the world and the second most common cancer diagnosed in the UK after breast cancer. In 2008, 40,806 new cases of lung cancer were diagnosed in the UK: 32,546 in England and 2403 in Wales. Lung cancer is rarely diagnosed in people aged <40 years and 86% of cases occur in people aged >60 years. In both men and women, smoking is the primary cause of lung cancer and prognosis is poor. Early-stage lung cancer is often asymptomatic, with two-thirds of patients diagnosed at a late stage.

In 2005 in the UK, the National Institute for Health and Care Excellence (NICE) produced comprehensive guidelines on the management of patients with lung cancer; these guidelines recommended chemotherapy for patients with non-small cell lung cancer (NSCLC): docetaxel (Taxotere®, Sanofi-aventis; DOC), gemcitabine (Gemzar®, Eli Lilly and Company; GEM), paclitaxel (Abraxane®, Celgene Corporation; PAX) or vinorelbine (Navelbine®, Pierre Fabre Pharmaceuticals Inc.; VNB) in combination with either cisplatin (CIS) or carboplatin (CARB) as standard first-line treatments for patients with locally advanced or metastatic disease. Further guidance has been published which recommends pemetrexed (Alimta®, Eli Lilly and Company; PEM) in combination with CIS as first-line treatment for patients with non-squamous locally advanced or metastatic disease and gefitinib (Iressa®, AstraZeneca; GEF) as a suitable first-line treatment for patients with epidermal growth factor receptor (EGFR) mutation-positive (M+) locally advanced or metastatic disease. The NICE guidelines for the diagnosis and treatment of lung cancer were partially updated in 2011. However, the current guidance on chemotherapy for patients with NSCLC has not been updated and there is therefore a need for the synthesis of current NICE guidelines with NICE guidance resulting from recent single technology appraisals. The objective of this report is to provide such a synthesis.

Objectives

The objective of the study was to evaluate the clinical effectiveness and cost-effectiveness of first-line chemotherapy currently licensed in Europe and recommended by NICE, for adult patients with locally advanced or metastatic NSCLC. The results in this report relate solely to first-line systemic therapy for patients with locally advanced or metastatic NSCLC. No inference should be drawn from them regarding chemotherapy in any other context; this includes adjuvant therapy, combination therapy (with radiotherapy or surgery) or second-line and maintenance therapy. It is also important to recognise that, as in the delivery of all clinical care, there is a need to tailor treatments to the needs of individual patients and this will include the exploration of options and consideration of the risks and benefits of the various treatments available by the clinician in consultation with his or her patients.

Methods

Search strategy

Three electronic databases (MEDLINE, EMBASE and The Cochrane Library) were searched from January 1990 to August 2010 for randomised controlled trials (RCTs), systematic reviews and economic evaluations.

Patient populations

Chemotherapy-naive adult patients with locally advanced or metastatic NSCLC were included.

Interventions and comparators
Studies that compared any first-line chemotherapy currently licensed in Europe and recommended by NICE were considered.

Outcomes
Data on any of the following outcomes were included in the assessment of clinical effectiveness: overall survival (OS), OS at 1 and 2 years, progression-free survival (PFS), time to progression (TTP), tumour overall response rate, quality of life (QoL) and adverse events (AEs). For the assessment of cost-effectiveness, outcomes included incremental cost per life-year gained and incremental cost per quality-adjusted life-year (QALY) gained.

Application of inclusion/exclusion criteria
Two reviewers independently screened all titles and/or abstracts including economic evaluations. The full manuscript of any publication judged to be relevant by a reviewer was obtained and assessed for inclusion or exclusion. Two reviewers assessed the relevance of each publication; any discrepancies were resolved by consensus and, where necessary, a third reviewer was consulted.

Data extraction and quality assessment
Data were extracted into a Microsoft Access 2007 database (Microsoft Corporation, Redmond, WA, USA). All trials were assessed for methodological quality using criteria based on the Centre for Reviews and Dissemination guidance. The results of clinical and economic data extraction and quality assessment are summarised in the tables and narrative description.

Evidence synthesis
Where appropriate, relative treatment effects for OS, PFS, TTP and survival risk at years 1 and 2 were estimated using a standard meta-analysis for head-to-head comparisons between interventions based on intention-to-treat analyses. Mixed-treatment comparison methodology was used for the clinical effectiveness outcomes of OS, PFS, TTP and survival risk at 1 and 2 years.

Results

Of the 193 identified trials published since 2000, 23 trials compared chemotherapy drug regimens that are currently licensed in Europe and are recommended by NICE in a monotherapy or in combination with a platinum (PLAT) drug for the first-line treatment of patients with locally advanced or metastatic NSCLC.

Seven economic evaluations were identified from a possible 15 potential publications.

Quality assessment
Overall, the quality of the included RCTs was poorer than expected: there were few trials with fully reported methods and the definitions of the health outcomes used often differed between trials.

Clinical effectiveness review: efficacy data
All 23 clinical trials were published between 2001 and 2010 and included a total of 11,428 randomised patients. Of the 20 multicentre trials, six were international; the three single-centre trials were based in Taiwan. Seventeen trials were assessed as being sufficiently powered to evaluate OS. Median follow-up of patients ranged from 8 to 45 months. Doses of chemotherapy drugs varied, median number of chemotherapy cycles ranged from 2.6 to 6 and chemotherapy treaments were administered either by intravenous (i.v.) infusion or orally.

When the three GEF trials were compared with the other included trials, the proportion of males to females was much less; the percentage of males in the GEF trials ranged from 21% to 37%. These three trials were conducted in East Asian countries and had somewhat different patient populations compared

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with the other trials. Two of these trials included only patients with EGFR M+ tumour status, and one trial included patients with pulmonary adenocarcinoma who were never-smokers or were former light smokers.

Twenty-three trials were included within the network of trials for the clinical analysis. The direct evidence for the NSCLC population with squamous disease included 18 trials (>7000 patients and >6000 deaths). These same 18 trials plus subgroup data from an additional two studies were included in the analysis of the NSCLC population with non-squamous disease. Participants of three studies, conducted entirely within East Asian countries, constituted the EGFR M+ NSCLC population. In general, there was consistency between the results of the direct meta-analyses and the mixed-treatment comparison analyses, and also very good consistency across individual trials in the within-group comparisons.

Among NSCLC patients with squamous disease, there were no statistically significant differences between any of the four chemotherapy regimens (DOC + PLAT, GEM + PLAT, PAX + PLAT, VNB + PLAT) in terms of increasing OS. However, both the direct and indirect evidence suggests a potential non-statistically significant advantage in terms of OS for GEM + PLAT [direct meta-analysis 1: hazard ratio (HR) = 1.08; 95% confidence interval (CI) 0.98 to 1.20] and for DOC + PLAT (direct meta-analysis 1: HR = 0.89; 95% CI 0.78 to 1.00; mixed-treatment comparison 1, HR = 0.92; 95% CI 0.81 to 1.03) compared with VNB + PLAT. Analyses of 1- and 2-year survival support this conclusion.

For patients with non-squamous NSCLC there is borderline statistically significant evidence to suggest that PEM + PLAT increases OS compared with GEM + PLAT (direct meta-analysis 1, HR = 0.85; 95% CI 0.73 to 1.00). However, there is no statistically significant evidence to suggest that PEM + PLAT compared with GEM + PLAT increases PFS (mixed-treatment comparison 1, HR = 0.85; 95% CI 0.74 to 0.98).

Among patients with EGFR M+ status, OS was not statistically significantly different in those treated with GEF and those receiving PAX + PLAT or in those treated with GEF compared with those treated with DOC + PLAT. There was a statistically significant improvement in PFS among those patients treated with GEF compared with those treated with DOC + PLAT or PAX + PLAT. However, there was significant quantitative heterogeneity between the two trials comparing GEF with PAX + PLAT, which requires further exploration.

It remains unknown whether or not the clinical effectiveness of PEM + PLAT is superior to that of GEF monotherapy for patients with non-squamous disease. The relative clinical effectiveness of PEM + PLAT in patients who are EGFR M+ is unknown.

Clinical effectiveness review: adverse events

Across all the chemotherapy arms of the included trials, the most common AEs were neutropenia, anaemia and leucopenia. Rates of haematological AEs were similar for all the chemotherapy drugs with the exception of GEF, which appears to be associated with a significantly lower severe AE rate than some of the other drugs. The trials often varied in the way that AEs were defined, measured and reported.

Clinical effectiveness review: quality of life

Twelve trials reported QoL outcomes using a variety of instruments/tools. Seven trials reported no significant difference in QoL and four trials reported some significant differences between treatment groups. A lack of reporting of QoL data is a feature of the great majority of trials assessing outcomes of treatment for patients with NSCLC. This, despite its relevance to patients and clinicians, is a major shortcoming of lung cancer research. Measuring QoL outcomes in patients with advanced NSCLC is difficult mainly because of the severity of symptoms, the side effects of chemotherapy and early deaths associated with NSCLC. However, the British Thoracic Oncology Group Trial 2 has shown that it is feasible to collect QoL data in patients with performance status (PS) 0–2, stage IIIB/IV NSCLC disease within a clinical trial setting.

Cost-effectiveness review: summary

None of the seven included studies were directly relevant to decision-making in the NHS because they are not UK focused and/or they do not estimate incremental cost-effectiveness ratios (ICERs) in terms of cost per QALY gained.

Summary of Assessment Group's cost-effectiveness results

A total of 12 first-line chemotherapy regimens were incorporated into the economic model developed by the Assessment Group (AG): five primary licensed products [DOC, GEM, PAX, VNB (i.v. and oral)] used in combination with either CIS or CARB, PEM in combination with CIS, and GEF monotherapy. First-line chemotherapy regimens with the same primary agent but different PLAT therapy differ only in terms of treatment costs. A lifetime perspective is taken in the model and costs and benefits are discounted at 3.5% per annum. In the base-case analysis, *British National Formulary* (BNF) prices are used and in the sensitivity analysis, electronic market information tool (eMIT) prices are used; probabilistic sensitivity analysis results are also provided.

Economic results: patients with squamous disease

The four third-generation chemotherapy agents, when used in combination with PLAT for first-line treatment of advanced or metastatic NSCLC, are often considered to exhibit similar effectiveness, when compared in terms of standard statistical measures (e.g. *p*-values). However, the mixed-treatment comparison analysis undertaken by the AG which informs the current model does indicate important differences which, when combined with differences in the management of the condition and acquisition cost, provide a basis for differentiating between treatment options and arriving at some robust conclusions:

- In both deterministic and probabilistic analyses for both the base-case and alternative pricing scenarios, VNB doublets yield the least patient benefit (as measured by expected discounted QALYs), and are not the least expensive option. As a result, VNB cannot be considered to provide either optimal effective or cost-effective chemotherapy treatment.
- PAX doublets are consistently minimum cost options and therefore represent the initial 'good value' treatment, to be supplanted only if an alternative option yields greater benefit at an acceptable 'willingness-to-pay' (WTP) threshold.
- The choice of preferred alternative main agent to PAX generally favours DOC over GEM as its greater effectiveness appears to outweigh the additional acquisition cost, although both lie on the efficiency frontier.

Economic results: patients with non-squamous disease

The addition of a PEM doublet to the four third-generation chemotherapy agents changes the relationship between the regimens, because of the clear outcome advantage of PEM therapy in terms of the improved expected survival of patients with non-squamous disease. However, the high price of branded PEM compared with the other drugs (in most cases available generically) means that PEM is preferred on cost-effectiveness grounds only if the WTP threshold is set > £37,000 per QALY (or £50,000 per QALY if eMIT prices are assumed). This means that PAX remains a viable treatment (and possibly GEM and DOC). However, VNB is clearly not cost-effective in either scenario.

Economic results: patients who are epidermal growth factor receptor mutation positive

The base-case analyses for GEF compared with the two chemotherapy doublets (PAX and DOC) for which evidence is available show poor cost-effectiveness for GEF. Results are improved somewhat by disaggregating the three GEF trials, but even then cost-effective ICERs (< £30,000 per QALY gained) are obtained only for the second alternative scenario [Western Japan Thoracic Oncology Group (WJTOG) trial only] based on the smallest RCT comparing GEF with the DOC + CIS doublet.

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Discussion

Using BNF prices the AG has demonstrated that CIS doublets are preferred to CARB doublets. For patients with squamous disease, moving from low to moderate WTP thresholds, preferred drugs are: PAX → GEM → DOC. For patients with non-squamous disease, a similar pattern of ranking applies: PAX → GEM → DOC. However, PEM + CIS has improved OS compared with all other recommended treatments in patients with non-squamous disease, but PEM + CIS is relatively expensive and a high threshold is required before PEM + CIS can be considered cost-effective (up to £35,000 per QALY gained). For patients with EGFR M+, comparing GEF to PAX and DOC yields very high ICERs. For all populations, using eMIT prices means that CARB doublets are generally preferred to CIS doublets and drug administration costs become more important than drug acquisition costs. The AG is aware that the economic results rely on the limited clinical data available. Modelling of costs and benefits reveals that there are often only slight differences between treatments in terms of clinical effectiveness yet when these differences are modelled over the longer term (>12 months) and the costs of the treatments are taken into consideration, then differences in cost-effectiveness begin to appear.

The treatment of patients with NSCLC is complex. In contrast to previous research, recent clinical effectiveness evidence from RCTs demonstrates that patient health outcomes depend not only on the treatment received but also on the characteristics of the patient population participating in the trial and of the cancer subtypes. Patients with NSCLC are not a homogeneous group; increasingly trials are distinguishing between three populations of patients (patients with squamous disease, patients with non-squamous disease and patients who are EGFR M+). The clinical effectiveness and cost-effectiveness evidence for each of the three patient populations needs to be reviewed separately.

As the prices of generic chemotherapy fall and new treatments become available, it is also prudent to consider cost-effectiveness using both BNF and eMIT prices. From the results of the economic evaluations described in this report it is clear that the size of the decision-makers' WTP threshold influences the range of treatments considered to be cost-effective.

Limitations

The limitations of the report can be summarised as follows: very few trials reported QoL data; AEs from the different trials were difficult to compare; CARB and CIS were treated as being similarly effective in the clinical analyses; and owing to the large volumes of data available for patients with lung cancer, the methods employed in the review do not always match the methods stated in the original protocol. Finally, the quality of the included trials was poorer than anticipated and this finding must be taken into consideration when interpreting the results of the clinical and economic analyses presented.

Conclusion

This comprehensive *Health Technology Assessment* review is unique to the field of NSCLC research in that it compares all of the regimens currently licensed in Europe and approved by NICE for the first-line systemic treatment of patients with advanced NSCLC. This review may assist clinicians to make decisions regarding the treatment of patients with advanced NSCLC as new evidence related to the important subgroups of patients becomes available in published form.

Research recommendations

The design of future lung cancer trials needs to reflect the influence of factors such as histology, genetics and the new prognostic biomarkers that are currently being identified. In addition, trials will need to be adequately powered so as to be able to test for statistically significant clinical effectiveness differences within patient populations. New initiatives are in place to record detailed information on the precise chemotherapy (and targeted chemotherapy) regimens being used, together with data on age, cell type, stage of disease and PS, allowing for very detailed observational audits of management and outcomes

at a population level. It would be useful if these initiatives could be expanded to include the collection of health economics data.

Implications for practice

Closer examination of clinical effectiveness and cost-effectiveness data means that we have been able to provide a comprehensive framework of information for three subpopulations of patients with NSCLC that clinicians can refer to as they attempt to balance patient factors, available treatments, treatment costs and AEs in their daily decision-making.

Concluding remarks

The completion of this review has taken a significant length of time and during that period there has been explicit acknowledgement in the published literature of the important differences in the characteristics of patients who previously were identified as having NSCLC. It is anticipated that no further RCTs will be carried out involving patients with NSCLC as a homogeneous group, but that consideration of the important patient subgroups will take precedence and allow for the development of more specialised and targeted treatments which, in turn, will require RCTs of increasingly sophisticated design.

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