A systematic review of the clinical effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer

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ABSTRACT

Our aim was to evaluate the clinical effectiveness of chemotherapy treatments currently licensed in Europe and recommended by the National Institute for Health and Care Excellence (NICE) for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). A systematic search of MEDLINE, EMBASE and the Cochrane Library for randomised controlled trials (RCTs) published from 2001 to 2010 was carried out. Relative treatment effects for overall survival (OS) and progression-free survival (PFS) were estimated using standard meta-analysis and mixed treatment comparison methodology. A total of 23 RCTs were included: 18 trials compared platinum-based chemotherapy, two compared pemetrexed and three compared gefitinib. There are no statistically significant differences in OS between any of the four third-generation chemotherapy regimens. There is statistically significant evidence that pemetrexed+platinum increases OS compared with gemcitabine+platinum. There are no statistically significant differences in OS between gefitinib and docetaxel+platinum or between gefitinib and paclitaxel+platinum. There is a statistically significant improvement in PFS with gefitinib compared with docetaxel+platinum and gefitinib compared with paclitaxel+platinum. Due to reduced generic pricing, third-generation chemotherapy regimens (except vinorelbine) are still competitive options for most patients. This research provides a comprehensive evidence base, which clinicians and decision-makers can use when deciding on the optimal first-line chemotherapy treatment regimen for patients diagnosed with locally advanced or metastatic NSCLC.

INTRODUCTION

Lung cancer is the second most common cancer diagnosed in the UK after breast cancer, with over 40 000 new cases being diagnosed in 2008.[1] Non-small cell lung cancer (NSCLC) accounts for approximately 84% of all lung cancer cases[2] and prognosis is poor; lung cancer is usually asymptomatic in the early stages and two-thirds of patients are diagnosed at a late stage (stages IIIB–IV) when curative treatment is not a viable option.[1] Patients with a performance status (PS) of 0–1 who are not eligible to receive potentially curative treatment such as surgery or radiotherapy, can receive chemotherapy, which could increase overall survival (OS) and progression-free survival (PFS), and improve health related quality of life (QoL).[3]

Our review focused on comparing all first-line treatments that are licensed in Europe and approved by the National Institute for Health and Care Excellence (NICE) for adult patients with locally advanced or metastatic NSCLC; currently, there is no available evidence base comparing all of these treatments. Recent clinical research[4 5] related to histology and genetics has demonstrated important differences within the population of patients with NSCLC. Our review is unique in its focus on the efficacy of first-line treatments in the subpopulations of NSCLC patients, specifically patients with squamous disease, patients with non-squamous disease, and patients who are EGFR M+.

This review was commissioned by the National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme. The review encompassed the clinical and cost effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic NSCLC; this paper summarises the findings of the clinical effectiveness review and provides a synopsis of the cost-effectiveness analyses.[6]

METHODS

Search strategy

A comprehensive strategy was employed to search MEDLINE, EMBASE and the Cochrane Library for English language trials published from 2001 to August 2010. Details of the search strategy are presented in supplementary online table S1. To ensure completeness of the review, the American Society of Clinical Oncology (ASCO) database was searched to identify any relevant trials from details of conference abstracts. Bibliographic searches of included papers were also performed.

Application of inclusion criteria

Two reviewers independently screened all titles and abstracts; full-text copies of potentially relevant citations were obtained and were assessed for inclusion by two reviewers. Where necessary, a third reviewer was consulted for consensus.

Inclusion of studies was limited to randomised controlled trials (RCTs) comparing first-line chemotherapy treatments for adult patients with locally advanced or metastatic NSCLC; treatments had to be currently licensed for use in Europe and recommended by NICE. Trials were included if OS or PFS/time to treatment progression (TTP) were reported. Abstract only publications were excluded.

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Data extraction and quality assessment

Data on the following were extracted into an ACCESS database: trial design, patient characteristics, intervention details such as chemotherapy schedule and mode of administration, and outcome data including median OS, median PFS/TTP, overall response rate, 1- and 2-year survival, adverse events (AEs) and QoL data. All RCTs were assessed for methodological quality using criteria based on the Centre for Reviews and Dissemination guidance[7] for undertaking reviews in healthcare. All data were extracted by one reviewer and independently checked for accuracy by a second reviewer; where necessary, consensus was achieved through consultation with a third reviewer.

Statistical analysis

To reflect current UK treatment pathways (see figure 1), analyses were undertaken and reported for three subpopulations of patients with NSCLC: patients with predominantly squamous disease, patients with predominantly non-squamous disease, and patients who were EGFR M+. In the main, all analyses were conducted on the total population according to randomisation; however, subpopulation data were included in our analyses if used previously for international or national decision making.

We assume that the results of all studies that do not differentiate between subpopulations are equally applicable to patients with squamous disease and non-squamous disease. Before adopting this approach, we identified four third-generation studies[8–11] which reported multivariate statistical testing and included histology as a candidate explanatory variable. From our critique of these studies, we concluded that histology did not have a significant influence on outcomes for patients with squamous or non-squamous disease. In this review, all data applicable to the squamous population were derived from mixed population studies; however, none of the studies included in the review investigated the use of chemotherapy solely for patients with squamous disease.

In terms of direct evidence syntheses, standard meta-analysis (MA) was undertaken for each pair-wise treatment comparison using the 'metan' command within STATA V.9.2.[12] For time-to-event outcomes (OS and PFS/TTP), the trial level estimate of log (HR) and its variance were extracted directly from trial publications if available. Additional data were requested whenever needed from the authors of trials in order to include as many relevant trials as possible in the MA. In the absence of direct estimates from published papers or requested from the authors, Kaplan-Meier (K-M) survival curves or log-rank statistics were used to estimate the required trial level log (HR) and its variance.[13 14] A random effects (frequentist) inverse variance weighted approach was used to pool estimates of log (HR) across trials.

An insufficient number of trials directly compared all chemotherapy treatment options and so multiple treatment comparison (MTC) methodology was undertaken in order to synthesise information on the relative efficacy of all included chemotherapy regimens. A Bayesian MTC framework was adopted to synthesise information on all chemotherapy technologies simultaneously using Markov chain Monte Carlo (MCMC) methods to estimate the posterior distributions for the outcomes of interest. WinBUGS V.1.4 statistical software[15] was used for the MTC analysis by adapting codes from the Multi-Parameter Evidence Synthesis Research Group (MPES).[16]

OS and PFS/TTP results were expressed as HRs with 95% CIs. Statistical heterogeneity was assessed by considering the χ^2 test for heterogeneity with a 10% level of significance, and the I2 statistic with a value of 50% representing moderate heterogeneity.[17 18]

RESULTS

Quantity and quality of included randomised controlled trials

As shown in figure 2, electronic searches identified 5378 unique citations. Initial screening identified 240 potentially relevant references which were obtained as full-text articles and were assessed for eligibility for inclusion. After the exclusion of trials which did not compare the relevant interventions, 23 trials[4 5 8–11 19–35] comparing chemotherapy drugs currently licensed in Europe and recommended by NICE for the first-line treatment of patients with locally advanced or metastatic NSCLC, were included for evidence synthesis.

Quality assessment results are presented in supplementary online table S2.[4 5 8–11 19–35] All trials reported the number of patients randomised, however only six RCTs[5 8 9 27 28 32 36] were assessed as adequately randomised with adequate concealment of allocation. All trials reported eligibility criteria; 20 trials reported detailed information about baseline comparability and three trials[20 24 34] partially reported information about baseline comparability, but only five trials achieved baseline comparability.[10 19 22 27 31] Although the majority of trials reported

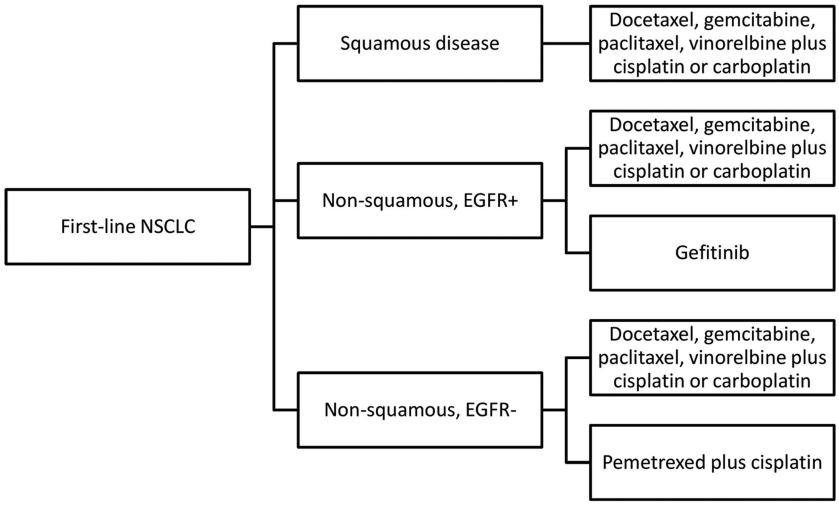

Figure 1 Treatment pathway.

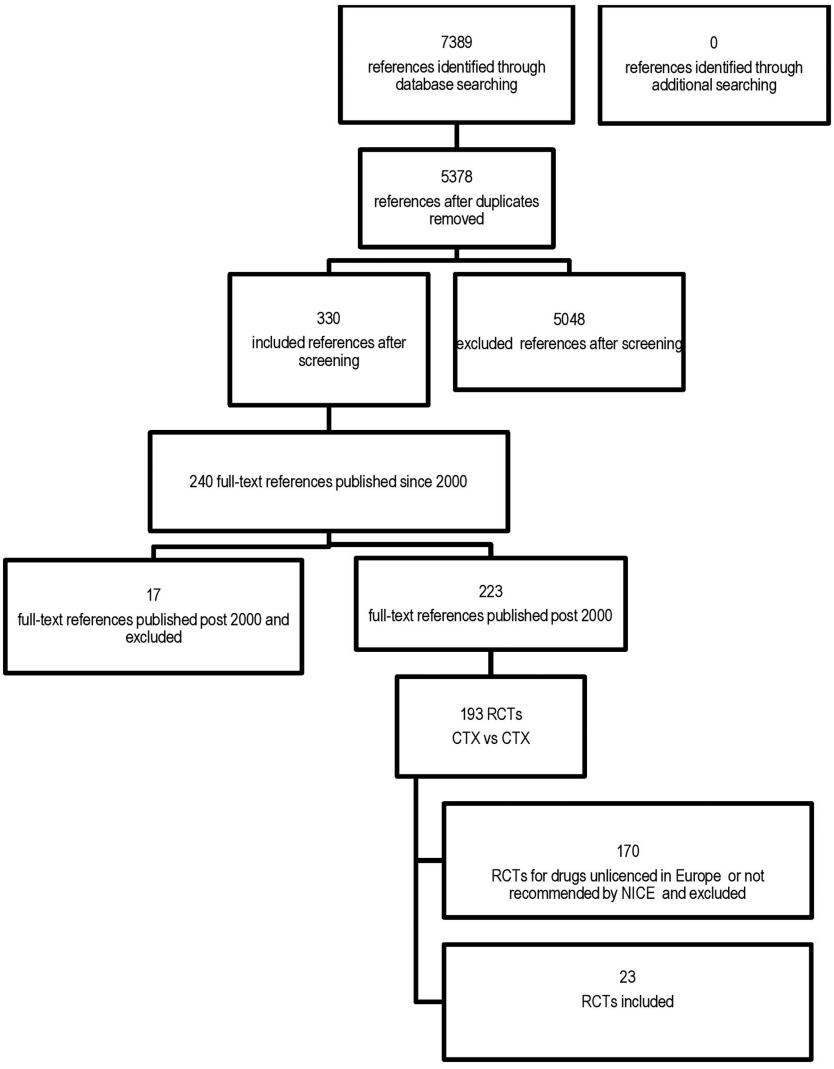

Figure 2 PRISMA flow diagram.[41] CTX, chemotherapy; NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial.

second-line chemotherapy, only one trial[20] was designed to consider second-line therapy. Seven trials[5 10 21 29–32] were reported as 'open' and it was assumed that assessors, administrators and patients were not blinded to treatment except for one trial where the radiologist was stated to be blinded.[31] Blinding of participants, investigators or outcome assessors was not reported in 16 studies.[4 8 9 11 19 20 22–28 33–35] The outcomes of over 80% of patients were assessed in all studies and all studies reported reasons for dropout; 10 trials[4 5 10 19 20 22 24 25 30 33] used an intention to treat approach to assess OS. Five of the trials appeared to report fewer outcomes than initially stated, thus indicating the possibility of selective reporting.[4 20 24 28 33]

Overall, the quality of the included RCTs was poor—few trials fully reported methods and the definitions of the health outcomes used often differed between trials.

Trial characteristics

The 23 trials were published between 2001 and 2010. Of the 20 multicentre trials, six had multiple international centres.[4 5 8 10 11 30] The three single-centre trials were all located in Taiwan.[19 22 35] There are five phase II trials,[19–23] 16 phase III trials[4 5 8–11 24–33] and two trials[34 35] with phase undefined. Ten trials[4 5 9 10 20 21 28–30 33] were funded solely by pharmaceutical companies, five trials[11 23 31 32 34] were funded by research grants, two trials[8 24] were funded by both pharmaceutical companies and research grants, and funding was not stated in six trials.[19 22 25–27 35] Seventeen trials[4 5 8–11 19 20 22 24 26–29 32–34] were sufficiently powered to evaluate OS, four trials[23 25 30 31] were inadequately powered and the power of two trials[21 35] was unclear. Median follow-up ranged from 11 to 40 months. Doses of chemotherapy drugs used varied, the median number of chemotherapy cycles ranged from 2.6 to 6, and the route of administration was intravenous or oral. All trial characteristics details are set out in supplementary online table S3.[4 5 8–11 19–35]

Patient characteristics

Overall, trial patients were generally younger, had better PS and less co-morbidity compared with patients typically treated in UK clinical practice. The majority of patients in the trials were male with adenocarcinoma stage IIIB or IV and of PS 1. The percentage of males within each trial arm ranged from 56% to 84% for trials with platinum-based regimens incorporating third-generation chemotherapy drugs. The number of patients randomised into individual trial arms ranged from 39 to 863 and median age ranged from 56 to 67 years.

Supplementary online table S4 presents all patient characteristics data.[4 5 8–11 19–35]

Categorisation of trials

Reporting of trial outcomes has been categorised in the tables as follows: patients with squamous disease, patients with non-squamous disease and EGFR M+ patients. All trial outcomes

data are shown in supplementary online table S5.[4 5 8–11 19–35] Eighteen trials[8–11 19–28 30 33–35] in the NSCLC population with squamous disease are included; all 18 trials report outcomes for a mixed population (ie, trials include patients with squamous and non-squamous disease). Therefore, the results of these 18 trials are also applicable to the NSCLC population with non-squamous disease. The outcomes for the NSCLC population with non-squamous disease are augmented by the addition of two trials[4 29] which report specifically on subgroups with non-squamous disease. In addition, outcomes for patients who are EGFR M+ are derived from three trials[5 31 32 36] and are categorised separately.

NSCLC population with squamous disease

Median OS was reported in all 18 trials and ranged from 6.2 to 15.4 months.[19 23] Median PFS/TTP was reported in all 18 trials and ranged from 3.0 to 8.4 months;[19 23] however, the definitions of PFS and TTP employed varied across trials.

One trial[10] demonstrated significantly favourable survival estimates in a comparison between two regimens. In this study,[10] patients in the docetaxel+cisplatin arm had a longer median OS compared to those in the vinorelbine+cisplatin arm. Two trials[19 34] demonstrated differences in PFS/TTP between regimens; in one trial[34] patients treated with gemcitabine+cisplatin had a significantly longer median PFS than those on paclitaxel+cisplatin, while in the other trial[19] it was demonstrated that patients treated with vinorelbine+cisplatin had a significantly longer median PFS than patients treated with paclitaxel+cisplatin.

NSCLC population with non-squamous disease

In the two RCTs comparing pemetrexed, median OS rates ranged from 7.5 to 11.8 months.[4 29] One trial[4] demonstrated a statistically significant difference in outcomes in patients with non-squamous disease who received pemetrexed+cisplatin compared with those receiving gemcitabine+cisplatin. Another trial[29] did not show any significant difference in OS when comparing pemetrexed+carboplatin with gemcitabine+carboplatin.

NSCLC population with EGFR M+ status

Three trials in the NSCLC population with EGFR M+ status were included, of which two[31 32] included patients with EGFR M+ status only, and the IPASS trial[5 36] which selected specific patients in order to yield a relatively high proportion of participants with EGFR M+ status. Where data are available, median OS ranged from 21.6 to 30.9 months.[5 32 36] There was no significant difference in OS when comparing gefitinib with paclitaxel+carboplatin in two trials[5 31 36] and there was no significant difference in OS between gefitinib and docetaxel+cisplatin in one trial.[32] In contrast, the PFS results show a statistically significant benefit for patients receiving gefitinib compared with paclitaxel+carboplatin, and with docetaxel+cisplatin in all three trials.[5 31 32 36]

Clinical effectiveness summary results

Results summaries for all pair-wise comparisons between interventions from the direct MA and the MTC primary analyses for the three NSCLC populations are presented in supplementary online tables S2–S4.[4 5 8–11 19–35]

NSCLC population with squamous disease

Eighteen trials[8–11 19–28 30 33–35] were eligible for inclusion in the MA and MTC analyses in the population with squamous disease, with 7382 randomised patients and 6081 deaths (table 1).[8–11 19–28 30 33–35] The evidence related to outcomes for patients with squamous disease demonstrates that there are no statistically significant differences in OS between any of the four third-generation chemotherapy treatments. However, direct and indirect evidence suggest a potential advantage in terms of OS for gemcitabine+platinum (MA: HR 1.08, 95% CI 0.98 to 1.20) and for docetaxel+platinum (MA: HR 0.89, 95% CI 0.78 to 1.00; MTC-1: HR 0.92, 95% CI 0.81 to 1.03) compared with vinorelbine+platinum, although this advantage is not statistically significant.

Only seven trials[8 19 20 22 23 26 34] were included in the PFS analysis and the majority of these trials used slightly different definitions of PFS. There was no evidence of any significant difference in PFS between the third-generation chemotherapy comparators.

A further seven trials[9–11 21 25 33 35] reported results for the outcome TTP; there was no evidence of any statistically significant differences in TTP.

NSCLC population with non-squamous disease

Analyses for OS were based on 20 trials[4 8–11 19–30 33–35] involving 9553 randomly assigned patients and 7608 deaths (table 2).[4 8–11 19–30 33–35] For patients with non-squamous disease, there is evidence that pemetrexed+platinum increases OS compared with gemcitabine+platinum (MA: HR 0.85, 95% CI 0.73 to 1.00; MTC-1: HR 0.85, 95% CI 0.74 to 0.98). There is no evidence to conclude that there is any statistically significant difference between any of the other chemotherapy treatments in terms of increasing OS for patients with non-squamous disease. Both the direct and indirect evidence suggest a potential advantage for gemcitabine+platinum compared with vinorelbine+platinum in terms of OS; however, this advantage is not statistically significant. Both the direct and indirect evidence suggest a potential advantage for docetaxel+platinum compared with vinorelbine+platinum in terms of OS; however, this advantage is borderline statistically significant (MA: HR 0.89, 95% CI 0.78 to 1.00; MTC: HR 0.92, 95% CI 0.81 to 1.03). The MTC analysis shows a statistically significant difference between paclitaxel+platinum and docetaxel+platinum (HR 0.79, 95% CI 0.66 to 0.93), but the results of MA were not statistically significant.

NSCLC population with EGFR M+ status

Analysis for OS was based on the results of three trials[5 31 32 36] involving 663 randomly assigned patients and 199 deaths (table 3).[5 31 32 36] For patients with EGFR M+ status, there is no statistically significant difference in OS between gefitinib and paclitaxel+platinum or between gefitinib and docetaxel+platinum. There is evidence of a statistically significant improvement in PFS with gefitinib compared with docetaxel+platinum. While there is also evidence of a statistically significant improvement in PFS with gefitinib compared with paclitaxel+platinum, the significant heterogeneity between trials means the PFS results should be viewed with caution.

Adverse events

This review focused on AEs that were categorised in the published trial reports as being grade 3/4. Across trials, AEs were reported in a disparate fashion that was not amenable to comparison. Table 4 shows the 'top ten' AEs that occur in the greatest proportion of patients across all arms that used each chemotherapy treatment; AE data were extracted from each trial, grouping similar AEs and calculating the weighted average of the proportion of each AE according to each chemotherapy treatment administered. Certain AEs were grouped together;

Table 1 MA and MTC results, NSCLC population with squamous disease

Reference treatment vs comparator	Number of data points (trials with head-to-head comparison)	Number of patients in reference treatment/ comparator	Number of events (deaths) in reference treatment/comparator	MA HR (95% CI) N=18	MTC HR (95% CI) N=18
Overall survival					
GEM+PLAT vs VNB+PLAT[8 9 21 25–28 35]	8	1075/1077	842/860	1.08 (0.98 to 1.20)	1.09 (0.99 to 1.19)
GEM+PLAT vs PAX+PLAT[9 11 23 28 33 34]	6	1245/1344	1053/1186	1.03 (0.94 to 1.13)	1.05 (0.96 to 1.15)
GEM+PLAT vs DOC+PLAT[34]	1	301/304	262/271	1.06 (0.89 to 1.28)	1.00 (0.88 to 1.13)
VNB+PLAT vs PAX+PLAT[9 19 24 28]	4	625/630	496/481	0.98 (0.83 to 1.16)	0.96 (0.86 to 1.08)
VNB+PLAT vs DOC+PLAT[10 20 22 30]	4	766/1175	607/920	0.89 (0.78 to 1.00)	0.92 (0.81 to 1.03)
PAX+PLAT vs DOC+PLAT[34]	1	602/304	538/271	0.98 (0.76 to 1.27)	0.95 (0.82 to 1.10)
Progression-free survival					
GEM+PLAT vs VNB+PLAT[8 26]	2	269/269	312*	1.09 (0.87 to 1.38)	1.06 (0.81 to 1.39)
GEM+PLAT vs PAX+PLAT[23 34]	2	350/656	142/304†	1.17 (1.00 to 1.36)	1.23 (0.94 to 1.62)
GEM+PLAT vs DOC+PLAT[34]	1	301/304	105/114	1.15 (0.96 to 1.37)	1.08 (0.79 to 1.45)
VNB+PLAT vs PAX+PLAT[19]	1	70/70	7/14†	**1.52 (1.06 to 2.17)**	1.16 (0.87 to 1.61)
VNB+PLAT vs DOC+PLAT[20 22]	2	168/165	92/86	0.92 (0.74 to 1.16)	1.02 (0.78 to 1.36)
PAX+PLAT vs DOC+PLAT[34]	1	602/304	130/263†	0.97 (0.75 to 1.24)	0.88 (0.62 to 1.21)
Time to tumour progression					
GEM+PLAT vs VNB+PLAT[9 21 25 35]	4	433/436	91†/82†	1.03 (0.90 to 1.18)	1.02 (0.83 to 1.25)
GEM+PLAT vs PAX+PLAT[9 11 33]	3	744/742	417†/423†	1.01 (0.90 to 1.13)	1.21 (0.73 to 1.99)
GEM+PLAT vs DOC+PLAT	0	No trial data	No trial data	No trial data	0.98 (0.62 to 1.52)
VNB+PLAT vs PAX+PLAT[9]	1	203/204	34†/37†	0.90 (0.64 to 1.28)‡	0.99 (0.77 to 1.28)
VNB+PLAT vs DOC+PLAT[10]	1	404/406	86†/88†	0.96 (0.70 to 1.31)‡	0.96 (0.65 to 1.43)
PAX+PLAT vs DOC+PLAT	0	No trial data	No trial data	No trial data	0.98 (0.6 to 1.55)

*In one trial PFS events were reported for both arms.
†Includes progressive disease (PD) only as PFS/TTP event (PD or death) not reported.
‡Direct evidence.
Bold text indicates statistically significant results.
DOC, docetaxel; GEM, gemcitabine; MA, meta-analysis; MTC, mixed treatment comparison; NSCLC, non-small cell lung cancer; PAX, paclitaxel; PLAT, platinum; VNB, vinorelbine.

Table 2 MA and MTC results, NSCLC population with non-squamous disease

Reference treatment vs comparator	Number of data points (trials with head-to-head comparison)	Number of patients in reference treatment/ comparator	Number of deaths in reference treatment/ comparator	MA HR (95% CI) N=20	MTC HR (95% CI) N=20
Overall survival					
GEM+PLAT vs VNB+PLAT[8 9 25–28 35 21]	8	1075/1077	842/860	1.08 (0.98 to 1.20)	1.08 (0.99 to 1.18)
GEM+PLAT vs PAX+PLAT[9 11 23 28 33 34]	6	1245/1344	1053/1186	1.03 (0.94 to 1.13)	1.06 (0.97 to 1.16)
GEM+PLAT vs DOC+PLAT[34]	1	301/304	262/271	1.06 (0.89 to 1.28)	0.99 (0.87 to 1.13)
GEM+PLAT vs PEM+PLAT[4 29]	2	1084/1087	755/772	0.85 (0.73 to 1.00)	**0.85 (0.74 to 0.98)**
VNB+PLAT vs PAX+PLAT[9 19 24 28]	4	625/630	496/481	0.98 (0.83 to 1.16)	0.92 (0.68 to 1.24)
VNB+PLAT vs DOC+PLAT[10 20 22 30]	4	766/1175	607/920	0.89 (0.78 to 1.00)	0.98 (0.87 to 1.09)
VNB+PLAT vs PEM+PLAT	0	No trial data	No trial data	No trial data	0.92 (0.82 to 1.03)
PAX+PLAT vs DOC+PLAT[34]	1	602/304	538/271	0.98 (0.76 to 1.27)	**0.79 (0.66 to 0.93)**
PAX+PLAT vs PEM+PLAT	0	No trial data	No trial data	No trial data	0.85 (0.63 to 1.16)
DOC+PLAT vs PEM+PLAT	0	No trial data	No trial data	No trial data	0.94 (0.81 to 1.09)
Progression-free survival					
GEM+PLAT vs VNB+PLAT[8 26]	2	269/269	312*	1.09 (0.87 to 1.38)	1.06 (0.78 to 1.66)
GEM+PLAT vs PAX+PLAT[23 34]	2	350/651	142/304†	1.17 (1.00 to 1.36)	1.23 (0.77 to 1.65)
GEM+PLAT vs DOC+PLAT[34]	1	301/304	105/114	1.15 (0.96 to 1.37)	1.08 (0.7 to 1.61)
GEM+PLAT vs PEM+PLAT[4]	1	1084/1087	NR	0.90 (0.79 to 1.02)	0.90 (0.53 to 1.52)
VNB+PLAT vs PAX+PLAT[19]	1	70/70	7/14†	**1.52 (1.06 to 2.17)**	1.16 (0.6 to 1.65)
VNB+PLAT vs DOC+PLAT[20 22]	2	168/165	92/86	0.92 (0.74 to 1.16)	1.02 (0.61 to 1.44)
VNB+PLAT vs PEM+PLAT	No trial data	No trial data	No trial data	No trial data	0.85 (0.42 to 1.51)
PAX+PLAT vs DOC+PLAT[34]	1	602/304	130/263†	0.97 (0.75 to 1.24)	0.88 (0.59 to 1.52)
PAX+PLAT vs PEM+PLAT	No trial data	No trial data	No trial data	No trial data	0.73 (0.42 to 1.53)
DOC+PLAT vs PEM+PLAT	No trial data	No trial data	No trial data	No trial data	0.83 (0.43 to 1.65)

*Number of events are for both arms.
†Includes progressive disease (PD) only as PFS event (PD or death) not reported.
Bold text indicates statistically significant results.
DOC, docetaxel; GEM, gemcitabine; MA, meta-analysis; MTC, mixed treatment comparison; NSCLC, non-small cell lung cancer; PAX, paclitaxel; PFS, progression-free survival; PEM, pemetrexed; PLAT, platinum; VNB, vinorelbine.

Table 3 MA and MTC results, NSCLC population with EGFR M+ status

Reference treatment vs comparator	Total deaths/patients in both arms	MA HR (95% CI) N=3	MTC HR (95% CI) N=3
Overall survival			
PAX+PLAT vs GEF[5 31 36]	199*/448	0.94 (0.74 to 1.18)	0.94 (0.67 to 1.3)
DOC+PLAT vs GEF[32]	NR/172	1.64 (0.75 to 3.58)†	1.64 (0.54 to 4.96)
PAX+PLAT vs DOC+PLAT	No trial data	No trial data	0.57 (0.18 to 1.81)
Progression-free survival			
PAX+PLAT vs GEF[5 31 36]	NR/488	**0.38 (0.24 to 0.60)**	**0.39 (0.29 to 0.52)**
DOC+PLAT vs GEF[32]	NR/172	**0.49 (0.33 to 0.73)†**	**0.49 (0.28 to 0.86)**
PAX+PLAT vs DOC+PLAT	No trial data	No trial data	0.79 (0.42 to 1.48)

*Overall survival events not reported by EGFR M+.
†Direct evidence.
Bold text indicates statistically significant results.
DOC, docetaxel; GEF, gefitinib; MA, meta-analysis; MTC, mixed treatment comparison; NR, not reported; NSCLC, non-small cell lung cancer; PAX, paclitaxel; PLAT, platinum.

'anaemia haemoglobin' was categorised into 'anaemia'; 'neutrophils' to 'neutropenia'; and 'sensory neuropathy', 'motor neuropathy' and 'neurotoxic effects' were all grouped into 'neuropathy'. Table 4 serves only to compare the profile of AEs within each chemotherapy regimen and should not be used to compare toxicities across the different drug regimens. Data show that neutropenia is the 'top' AE associated with vinorelbine, paclitaxel and docetaxel; granulocytopenia is the 'top' AE associated with gemcitabine and pemetrexed. Neutropenia, leucopenia and granulocytopenia all describe a fall in white blood count and so incidence rates of these AEs are similar across all the chemotherapy drugs with the exception of gefitinib which appears to have a different toxicity profile; the 'top' AE for gefitinib is aminotransferase elevation.

Quality of life

Only 12 trials[5 8–11 19 22 24 27–30 36] reported outcomes relating to QoL, with QoL being the primary outcome in two trials.[8 29] MA was not performed due to limited data and variability in the outcome assessment measures reported. The paucity of data available means no firm conclusions can be drawn from the trial evidence described in the studies. The included trials used a number of standardised measurement tools: the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30[37] and the lung cancer-specific module QLQ-LC13[38] were used in three trials,[8 9 27] the Lung Cancer Symptom Scale (LCSS)[39] in four trials,[10 19 22 30] and the Functional Assessment of Cancer Therapy (FACT-L)[40] in three trials.[5 24 28 36]

Eight[8 19 22 24 27–30] trials did not report any significant difference in QoL between treatment groups. Four trials[5 9–11 36] reported some significant differences between treatment groups for QoL; in one trial[9] results after two cycles of chemotherapy favoured the paclitaxel+carboplatin arm, whereas results after four cycles favoured the vinorelbine+cisplatin arm.

SYNOPSIS OF COST EFFECTIVENESS

Background

This review aimed to assess the relative cost effectiveness of four platinum-based chemotherapy regimens for the treatment of

Table 4 Top 10 adverse events by chemotherapy regimen

DOC+PLAT	GEM+PLAT	PAX+PLAT	PEM+PLAT	VNB+PLAT	GEF
Neutropenia 71.4%	Granulocytopenia 48.8%	Neutropenia 62.5%	Granulocytopenia 37.9%	Neutropenia 68.3%	Aminotransferase elevation 33.8%
Leucopenia 43.5%	Asthenia 40.3%	Leucopenia 31.9%	Blood transfusions 26.9%	Leucopenia 47.2%	Appetite loss 5.3%
Weakness 16.0%	Neutropenia 36.4%	Weakness 14.5%	Infection 16.4%	Oedema 24.0%	Rash/acne 3.3%
Pneumonitis 11.5%	Thrombocytopenia 34.6%	Cancer pain 13.2%	Neutropenia 15.1%	Anaemia 19.3%	Toxic deaths 3.1%
Anaemia 11.2%	Anorexia 27.0%	Nausea 10.3%	Alopecia 11.9%	Phlebitis 15.7%	Diarrhoea 3.1%
Asthenia 10.2%	Leucopenia 20.1%	Anaemia 10.0%	Leucopenia 8.2%	Nausea/vomiting 11.5%	Neutropenia 2.8%
Nausea 9.9%	Transfusion 18.5%	Lethargy 9.4%	Thrombocytopenia 8.1%	Vomiting 10.3%	Pneumonitis 2.6%
Vomiting 9.8%	Alopecia 17.2%	Thrombocytopenia 8.3%	Anaemia 7.0%	Nausea 9.9%	Fatigue 2.5%
Cancer pain 8.4%	Weakness 17.0%	Neuropathy 7.9%	Fatigue 6.7%	Asthenia 9.4%	Infection 1.8%
Infection 7.5%	Anaemia 16.5%	Vomiting 7.4%	Nausea 6.2%	Pain 8.3%	Anaemia 1.6%

DOC, docetaxel; GEF, gefitinib; GEM, gemcitabine; PAX, paclitaxel; PEM, pemetrexed; PLAT, platinum; VNB, vinorelbine.

advanced or metastatic NSCLC (docetaxel, gemcitabine, paclitaxel or vinorelbine in combination with either cisplatin or carboplatin) and two additional treatments for specific subgroups of patients with NSCLC (pemetrexed in combination with cisplatin for patients with non-squamous disease and single agent gefitinib for patients who are EGFR M+).

Methods

Health outcomes and costs were modelled in three populations (squamous disease, non-squamous disease and EGFR M+) from a UK perspective. Regimens indicated for treating patients in each population were compared in terms of life years, quality adjusted life years, and healthcare and personal social care costs. Data from published RCTs with 24 months of follow-up were combined to generate typical non-linear temporal trajectories for each treatment option for OS and PFS, which were mutually calibrated using HRs at 12 months from the MTC described above. A cohort simulation model was developed to project patient experience and costs weekly, for 10 years, assuming up to two lines of chemotherapy. Deterministic and probabilistic incremental cost-effectiveness ratios (ICERs) were obtained for each population, using published list drug prices (base case) and also average health service contract drug prices.

Results

NSCLC population with squamous disease

In the squamous disease population, vinorelbine (oral or intravenous) doublets were shown not to be cost effective in either price scenario due to relatively poor outcomes. Paclitaxel, gemcitabine and docetaxel all lie on the efficiency frontier, but ICERs comparing interventions with better outcomes to paclitaxel exceed levels considered to be cost effective in the UK. The choice of platinum compound changes from cisplatin (base case) to carboplatin when contract drug prices are used, indicating that when drug costs are reduced, the location (and therefore cost) of administration influences cost-effectiveness estimates.

NSCLC population with non-squamous disease

In the non-squamous population, pemetrexed+cisplatin was shown to be a valid comparator to standard treatments and provides strong evidence of improved OS. However, its much higher price leads to non-competitive cost-effectiveness results.

NSCLC population with EGFR+ status

Evidence was found that EGFR M+ patients have a better prognosis than other NSCLC patients; this means that gefitinib could only be compared with two standard treatments through evidence from three small trials which recruited from this specific patient subgroup. As there is currently no evidence of OS advantage, at the current price paid by the UK NHS, gefitinib does not appear to be cost effective compared to docetaxel or paclitaxel doublets.

Conclusions

The advent of routine histological and genetic testing in lung cancer patients and the introduction of widespread low-priced generic versions of standard chemotherapy products have altered the nature of the decision problem, and placed new branded drugs (pemetrexed and gefitinib) at a clear economic disadvantage. With the exception of pemetrexed, the differences in outcomes between the available treatment options are modest and may not be sufficient to influence clinicians in their choice of medication. However, the consistently poor performance of vinorelbine therapy may be an exception.

DISCUSSION

Summary of results

This is the first comprehensive systematic review of all first-line chemotherapy treatments currently licensed for use in Europe and recommended by NICE for adult patients with locally advanced or metastatic NSCLC. This review highlights that research in this area is evolving rapidly with advances seen in relation to subgroups defined by histology and genetic factors within the NSCLC population. Our results show that treatment effects differ for different subpopulations of patients with NSCLC.

Generalisability of results

In earlier trials that assessed the clinical effectiveness of third-generation chemotherapy drugs, there was very little analysis of outcomes by factors such as histology or genetic markers and patients with NSCLC were classed as a homogeneous patient population. However, it is now accepted that NSCLC patients can be divided into at least three subpopulations: patients with squamous disease, patients with non-squamous disease and EGFR M+ patients. Our comparisons of available drugs for different subpopulations of patients with NSCLC are therefore extremely timely and should prove useful for decision-makers.

The evidence relating to patients with EGFR M+ status is based on the results from three trials[5 31 32 36] conducted in East Asian countries. It is questionable whether the results of these trials are generalisable to UK clinical practice as evidence suggests that East Asian populations with NSCLC have a more favourable prognosis compared with non-East Asian populations.[41] EGFR mutation rates are likely to differ between countries (in Europe and the UK estimated EGFR M+ rates are low compared to Asian countries),[42 43] although the actual response to chemotherapy may not differ in patients with the same mutation status. Evidence from our review shows that patients who are EGFR M+ have improved OS outcomes compared to all other patients. As yet there are no relevant UK-based trial data for patients with EGFR M+ status; this is not surprising as only a small proportion of UK patients participate in international RCTs. In trials where ethnicity is not a risk factor for disease, this is less of a problem when considering the generalisability of results.

Clinical effectiveness results relating to the elderly population with NSCLC may be under-represented by the findings of the review. The majority of trials have an upper age limit for entry, whereas in clinical practice a substantial proportion of patients are over 75 years of age. The majority of published trials focus on fitter populations with less co-morbidity than the average UK patient with NSCLC. In addition, single-agent regimens were excluded from the review as none of these are currently licensed for single-agent use. However, NICE clinical guidelines[3] state that docetaxel, gemcitabine, paclitaxel and vinorelbine can be administered as single agents if patients are intolerant of a platinum-based regimen, and this may include a larger proportion of elderly patients.

Strengths and limitations

Due to the large volume of related literature in this field, pragmatic decisions were made about the inclusion criteria and the focus of the data analyses was restricted to trials published after 2000. No direct evidence was identified for six pair-wise comparisons of chemotherapy drugs, which was a limitation; however, a particular strength of this review is its use of indirect evidence from MTC analyses to compare relative treatment

effects across all first-line chemotherapy regimens that are licensed in Europe and recommended by NICE for patients with NSCLC. The results of comparisons which demonstrate borderline statistically significant results should be treated with caution and used to indicate possible differences in chemotherapy treatments that should then be assessed by a formal trial (ie, viewed as research generating) and should not be used alone to justify changes in clinical practice.

This report was limited in its analyses of AEs mainly because trials varied in the way AEs were defined, measured and reported. Reporting of AEs in RCTs needs to be standardised and reported consistently to allow future comparisons. Further research is required regarding the clinical significance of any of the reported AEs, as well as their significance to patients in terms of QoL. In addition, the introduction of new treatments with differing AE profiles needs to be considered. OS is an important outcome in deciding which chemotherapy drug a patient should receive, but this must be considered alongside the possible AEs and the symptomatic benefits of therapy. A lack of reporting of QoL data is a feature of the great majority of trials assessing outcomes of treatment for patients with NSCLC, and is a major shortcoming of lung cancer research despite the relevance and importance of QoL to patients and clinicians.

Carboplatin and cisplatin were grouped together and considered as 'platinum' and treated as similarly effective for the purpose of analysis. This decision was made following discussions with clinicians and was, in part, based on NICE guidelines[3] which recommend that either carboplatin or cisplatin may be administered depending on the balance of toxicity, efficacy and convenience for patients. It is noted that the results of recent meta-analyses[44 45] suggest that cisplatin delivers greater efficacy than carboplatin, and that subsequently use of cisplatin has increased; however, clinical advice from experts confirms that clinical practice in the UK is still split between the two drugs. The results of the BTOG2 trial[46] will help to clarify the evidence regarding the relative efficacy of cisplatin and carboplatin in terms of survival, QoL and the costs associated with each drug and its delivery.

Overall conclusions

This review provides a comprehensive evidence base which clinicians and decision-makers can use when deciding on the choice of first-line chemotherapy for an individual patient diagnosed with locally advanced or metastatic NSCLC. This systematic review is unique to the field in that it directly considers and compares all six chemotherapy treatments currently licensed in Europe and approved by NICE for the first-line treatment of adult patients with NSCLC. The results of the review highlight that from a clinical perspective, when examining data from patients with NSCLC, it is often difficult to distinguish between approved treatments in relation to their clinical effectiveness and so the decision about which drug to use will be based on clinicians' judgement and experience. However, the results of the economic analysis that was carried out alongside this clinical review reveal a somewhat different picture. As many of the older treatments are now off patent, they are relatively less expensive compared to the newer (and, in most cases, no more effective) treatments; this means that their cost effectiveness is more easily demonstrated at lower willingness to pay thresholds.

This review highlights the fact that research in this area is now predominantly focussed on histological subpopulations of NSCLC as well as molecular profiling within the NSCLC population. Eighteen out of 23 included trials investigated the treatment of any patient with NSCLC; only recently have trials included and/or reported their results using subpopulations. Recruitment into NSCLC trials will continue to change dramatically over the coming years when further subpopulations are taken into consideration and targeted agents are introduced.

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