ORA cover sheet

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Primary author	
Contact for Rx Communications	Emma Houghton tel (direct): +44 (0) 1352 706191 fax: +44 (0) 1352 756260 email: emma.houghton@rxcomms.com
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Indirect Comparison of Pemetrexed plus Cisplatin with Other Platinum-based Therapies for First-line Advanced Non-small Cell Lung Cancer

Author(s): J. Vansteenkiste[1], L. Eckert[2], J. Arellano[3], F. de Marinis[4], J-Y. Douillard[5], M.J Edelman[6], C. Leteneux[3], P. Lianes[7], A.M. Liepa[8], R.B. Natale[9], R.A. Stahel[10], R. Launois[2]

Author affiliation(s): [1]University Hospital Gasthuisberg, Leuven, Belgium; [2]REES France, Paris, France; [3]Lilly Research Centre, Surrey, UK; [4]San Camillo-Forlanini Hospitals, Rome, Italy; [5]Centre R Gauducheau, Saint-Herblain, France; [6]University of Maryland Greenebaum Cancer Center, Baltimore, USA; [7]Hospital de Mataró, Barcelona, Spain; [8]Eli Lilly, Indianápolis, US; [9]Cedars-Sinai Comprehensive Cancer Center, Los Angeles, USA; [10]University Hospital, Zurich, Switzerland

Corresponding author: <<**Please indicate the corresponding author and provide address, fax, phone and e-mail details**>>

Address:

Phone:

Fax:

Email:

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Abstract

Estimated word count: 250

Introduction: Pemetrexed is a multi-targeted anti-cancer anti-folate agent that has recently been approved in the United States and Europe for use in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a predominantly non-squamous histology, based on results of a phase III randomized controlled trial that compared pemetrexed and cisplatin (XP) with gemcitabine and cisplatin. To date, pemetrexed has not been compared with other currently recommended treatment regimens in randomized controlled trials.

Methods: We conducted a systematic review of the literature and conducted an indirect analysis, using a mixed treatment comparison model utilizing Bayesian techniques, to assess the efficacy and safety of XP relative to other platinum-based regimens used in the first-line treatment of advanced NSCLC.

Results: We identified 27 published trials that included 19 different chemotherapy regimens and more than 13,000 patients that contributed to the analysis. Our analyses found no evidence that XP differs significantly in terms of efficacy and tolerability from other chemotherapy regimens in the first-line treatment of patients with advanced NSCLC of various histologies. Efficacy differences by NSCLC histology could not be determined by this methodology due to a lack of published data for most studies. Trends for differences in toxicity were detected with neutropenia and febrile neutropenia favouring XP and nausea/vomiting favouring comparator regimens.

Conclusions: Based on these results and those of other studies assessing pemetrexed, XP can be considered a suitable first-line regimen for the treatment of patients with advanced non-squamous NSCLC.

Introduction

Word count: 672

Lung cancer is one of the most common malignancies, globally accounting for 1.2 million new cases annually and 17.8 per cent of all cancer deaths (WHO 2008). Each year, 900,000 men and 330,000 women worldwide are diagnosed with lung cancer, with smoking causing more than 80% of lung cancer cases in men and 45% of cases in women (>70% of cases in women in North America and Northern Europe). In both men and women, the incidence of lung cancer is low in those aged <40 years, and increases up to age 70 or 75 years (WHO 2008). Non-small cell lung cancer (NSCLC), comprising squamous cell carcinoma, adenocarcinoma and large cell carcinoma, accounts for about 80% of lung cancers (Travis et al. 1995). Approximately 75% of newly diagnosed patients have at least advanced NSCLC (stage IIIA or IIIB) of whom two-third have advanced metastatic disease (stage IV). Chemotherapy is recommended for many patients with non-resectable stage III or IV disease provided they have a good performance status (PS). Stage IIIB and IV NSCLC are generally not considered to be curable, with low five-year survival rates. However, chemotherapy can be useful for improving patients' quality of life and may offer a modest survival benefit.

Published guidelines universally emphasize that recommended chemotherapy in the first-line treatment of advanced NSCLC is based on a combination of platinum drug and a third-generation drug (NICE 2005; D'Addario et al. 2008; Pfister et al. 2004; ACCP 2007; National Health and Medical Research Council 2004). 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. It inhibits thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase, which are key folate-dependent enzymes for the de novo biosynthesis of thymidine and purine nucleotides (Shih et al. 1997). In 2004,

pemetrexed was approved by the United States Food and Drug Administration and the European Medicines Agency as monotherapy for patients with NSCLC previously treated with chemotherapy following results of the study of Hanna and colleagues (2004). In 2008, pemetrexed plus cisplatin was approved for use in the initial treatment of patients with locally advanced or metastatic NSCLC based on a phase III randomized controlled trial that compared pemetrexed plus cisplatin (XP) with an accepted current standard of care gemcitabine plus cisplatin (GP) (Scagliotti et al. 2008). These NSCLC indications are limited to patients with non-squamous histology based on prospective analysis of data from the trial by Scagliotti and colleagues (2008) and on retrospective analysis of data from the trial by Hanna and colleagues (Peterson et al. 2007). Given the lack of head-to-head trials comparing XP with platinum-based combinations other than the comparison with GP (Scagliotti et al. 2008), a systematic review of the literature was conducted to allow indirect comparison to assess the efficacy and safety of XP relative to other regimens commonly used in the first-line treatment of advanced NSCLC. This analysis was performed before the indication for XP in NSCLC was limited to patients with non-squamous histology and therefore does not exclude patients with squamous NSCLC.

Materials and Methods

Word count: 1333

Data selection

Clinical trials of XP in NSCLC were retrieved following a search of the MEDLINE electronic database from 1995 to September 2007 and, to ensure the most recent evidence was included, the 2007 American Society of Clinical Oncology (ASCO) and International Association for the Study of Lung Cancer (IASLC) congress websites. Similarly, these sources were searched to identify randomized controlled trials for the drugs previously selected by an international group of experts as pertinent comparators of pemetrexed in the first-line treatment of NSCLC (gemcitabine, intravenous vinorelbine, oral vinorelbine, docetaxel, paclitaxel, erlotinib [including articles investigating single agent therapy], gefitinib [including articles investigating single-agent therapy], and bevacizumab). The research string for MEDLINE searches used the MeSH terms: carcinoma, non-small-cell lung, pemetrexed, docetaxel, gemcitabine, paclitaxel, vinorelbine, erlotinib, bevacizumab, gefitinib, phase II or III clinical trial, controlled clinical trial, multicenter study and randomized controlled trial. The treatment regimens identified from the literature searches for inclusion in the analysis (and their abbreviations) are presented in table 1.

Publications were first selected by title, then by abstract. Remaining publications that could not be selected or rejected based on title or abstract were read entirely to determine which should be selected for data extraction. Studies were included if they met the following criteria: randomised study, involved at least one of the regimens of interest, patients were receiving first-line treatment for stage IIIB or IV NSCLC, and patients had a PS ≤ 2 (or ≥ 60 if Karnofsky scale). Studies were excluded if dose-finding, using radiotherapy as a comparator, focusing on patients with a PS = 2 only or elderly only, or published in a foreign language that no one from the research team

could translate (for example, Chinese). In addition, studies were excluded if the data they contained did not add to the network of evidence (Figure 1).

Recently published meta-analyses, identified by a MEDLINE search, were used to assess whether published synthesis of evidence would reinforce or challenge the findings of this analysis and to provide data missing from primary publications. Two meta-analyses of interest were identified (Pujol et al. 2006; Le Chevalier et al. 2005).

Endpoints of interest

The endpoints of interest were overall survival, time to progression (TTP), 1-year survival rate, overall response rate and selected severe (grade 3 and 4) toxicities (febrile neutropenia, neutropenia, nausea/vomiting, thrombocytopenia, anaemia, and diarrhoea). Other toxicities were also considered but could not be included, as insufficient data were available to allow analysis. Because of differences between published trials regarding the definition of some outcomes, a number of assumptions were made to reduce the amount of missing data for the corresponding outcomes and to maximise the relevance of the analyses performed: TTP and progression-free survival (PFS) were considered to provide similar hazard ratio information (when both TTP and PFS were provided, TTP was used); when nausea and vomiting were reported separately, the maximum of the two percentages was used to impute the variable nausea/vomiting; grade 3 or 4 platelet count decrease was considered grade 3 to 4 thrombocytopenia and was termed severe thrombocytopenia; grade 3 to 4 haemoglobin count decrease was considered grade 3 to 4 anaemia and was termed severe anaemia; grade 3 to 4 granulocyte count decrease was considered grade 3 to 4 neutropenia and was termed severe neutropenia; grade 3 to 4 febrile neutropenia is considered equivalent to grade 3 to 4 fever and neutropenia. These assumptions were made with consensus of 7 international experts and further tested in sensitivity analyses.

Some of the overall survival and TTP results that were not reported as hazard ratios could be imputed either using the Parmar method (Parmar et al, 1998) or by using the hazard ratio calculated in the Le Chevalier meta-analysis (Le Chevalier, 2005). Variations in doses for regimens of interest were ignored when pooling data across studies, with exception of paclitaxel infusions (24 hours versus ≤3 hours).

Modelling technique and Statistical Analysis

A mixed treatment comparison model was implemented to indirectly compare the efficacy and toxicity profile of XP with other first-line drug combinations for the treatment of NSCLC. The method used is an extension of the classical meta-analysis to broader evidence structure and allows indirect comparisons between treatments of interest (Figure 1 shows the network of evidence for this analysis). For example, a meta-analysis provides a synthesis of trials comparing drug regimes A *vs.* B and A *vs*. C, but will not provide data concerning B *vs.* C if there were no trials comparing regimens B and C. Using the mixed treatment model, it is possible to compare regimens B *vs.* C by using results of a study comparing A to B and those of another study comparing A to C. If the populations, setting and other variables of both studies are sufficiently similar, the effect of A should be the same in both studies (random variation notwithstanding). By analysing the relative effect of B *vs*. A and C *vs*. A, the relative efficacy of B *vs*. C can be estimated by using A to link the two treatments.

The mixed treatment comparison model utilized Bayesian techniques to compare the different treatments of interest. The model was initially run using overall response rate, as this endpoint had data from all 27 studies and for all 19 treatments included in the analysis, as both a fixed and random effect model. When residual deviance, Deviance Information Criteria and confidence intervals for results were considered, a random effects model was found to provide the most accurate estimates. Thus a mixed treatment comparison model, using random-effect, was utilised to compare treatments across clinical trials (Lu & Ades 2004). Odds ratios for each treatment were analysed

assuming a binomial distribution using the methods of Lu and Ades (2004), whereas logarithms of hazard ratios were analysed assuming a normal distribution based on the work of Spiegelhalter and colleagues (1996, 2004) and Lu and Ades (2004). Results are presented with 95% confidence intervals (CI).

Variance modelling was used when trials with more than two arms were included using the methods of Higgins and Whitehead (1996) and Whitehead (2002).

Hazard ratios for regimens compared in each study were extracted for the endpoints overall survival and TTP. Hazard ratios were calculated for XP versus comparator regimens using data from the mixed treatment comparison model. Hazard ratios for overall survival and TTP were computed with a mortality endpoint and XP was taken as the denominator. For overall response rate, 1-year survival rate, and the incidences of toxicities, absolute rates for each regimen from individual studies were extracted and pooled data for each regimen were calculated. Odds ratios for XP versus each comparator regimen were estimated using the mixed treatment comparison model. Odds ratios for one-year survival rate and overall response rate were computed with a survival endpoint and XP was taken as the denominator.

WINBUG software was used for all analyses. This software automatically derived the median values for endpoints of interest.

Sensitivity analyses

Sensitivity analyses were performed to assess the robustness of results. These analyses were performed on the probabilities that pemetrexed was better than each comparator regimen for overall survival and TTP and the probabilities that each treatment would produce the highest 1-year survival rate or response rate or lowest toxicity by adding co-variables into the model (adjusted analyses).

The adjusted analyses used meta-regression to simultaneously compare several treatments and adjust for study-level co-variables. The co-variables used were:

percentage of PS=2 patients, gender, percentage of patients with stage IV disease and percentage of patients with a squamous histology (chosen a priori because they were potential confounding factors). The percentage of patients with a squamous histology was included as a potential confounding factor because bevacizumab studies generally excluded patients with this histology. To reduce bias, when a publication did not mention one variable, the imputed value was the weighted average of the values extracted from publications where these data were available; the weights being equal to the number of patients in each study.

Study quality

Study quality was assessed using the European Lung Cancer Working Party (ELCWP) scale (Berghmans et al. 2003). It is composed of 2 groups of items assessing protocol design (number of participating centres, selection criteria, randomisation method, treatment description, work-up, evaluation criteria and statistical methods) and analysis performance (analysis timing, eligible patients characteristics, survival, brain metastases incidence, neurologic toxicity, prognosis factor for survival, prognosis factor for brain metastases, discussion). The global quality score was obtained by summing the score for each item: a score of 2 was given if the item was correctly described, 1 if the item was present but with no precise description and 0 if the item was absent or incorrectly described, to give a maximum score of 88.

Results

Estimated word count: 1215

Literature searches identified 959 potentially relevant publications involving possible comparator regimens for XP. Of these, 163 articles were retrieved for abstract reading, resulting in 52 references being selected for full text reading. Of these, 26 were excluded because they included patients with stage IIIA disease (n=10), evaluated treatments that could not be linked to other treatments in the analysis (n=11), reported results of a study already included (n=1), were not randomised (n=1), or had methodological problems (n=2) (see Appendix 1 for selection tree). Concerning the evidence available for XP in NSCLC, a total of 23 publications were retrieved from the MEDLINE search. Only one of the randomised first-line trials included a non-pemetrexed chemotherapy regimen (GP) and could be considered (Scagliotti et al. 2008) for inclusion in the analysis.

Table 2 summarises details of the 27 randomized controlled studies and the patients included in this analysis. A total of 13,064 patients with stage IIIB or IV NSCLC treated with a first-line chemotherapy and who complied with inclusion criteria were included in these analyses. The number of patients from each study varied from 98 to 1,725. Distribution of patient characteristics differed from study to study, particularly in terms of severity of disease and histology. However, study quality was homogeneous if the study by Manegold et al. (2007) is not considered. This study has a quality score of 17% (the median quality score was 58.3%), which was not surprising given that this was not a full publication but an abstract presented at ASCO 2007.

Initial analyses of between-study variance in response rate showed study heterogeneity of 0.17 (95% confidence interval (CI): 0.007-0.37) supporting use of a random effects model, which was used for the full analysis.

Overall survival

Table 3 summarises estimated hazard ratios, where available, for each of the 18 trials from which these data could be extracted or imputed. In most instances, an adjusted hazard ratio was reported. Modelling results showed that, overall, the estimated hazard ratios for comparators versus XP varied between 0.89 and 1.16 (Figure 2). Although survival tended to favour XP numerically for all but two comparisons (versus bevacizumab + paclitaxel + carboplatin [BTC] and vinorelbine + cisplatin [VP]), no regimen was statistically different from XP (Figure 2).

Sensitivity analyses

Results of sensitivity analyses showed that findings were generally consistent when adjusting for potential confounding variables or subgroups of studies. The only changes in relative efficacy observed were that VP no longer tended to be numerically better than XP when analyses were adjusted for stage IV disease, and XP no longer tended to be better than docetaxel + carboplatin (DC) when analyses were adjusted for PS = 2 or squamous cell histology.

Time to progression

Where available, TTP data for individual trials are presented in Table 3 (data could be extracted or imputed for 15 studies); because of the network of evidence, some associations could not be analysed because they were not linked to other treatments.

Figure 3 shows that the hazard ratios between comparators and XP varied from 0.63 to 1.22, with most favouring the comparator regimen (no trend was significant). Confidence intervals are wide due to the limited data for most comparators.

Sensitivity analyses

Sensitivity analysis showed results consistent with those of the primary analysis. Hazard ratios did not differ significantly between XP and comparators, and confidence

intervals remained broad in all analyses. The only change in relative efficacy observed was that TC no longer tended to be better than XP when analyses were adjusted for squamous cell histology.

One-year survival

Available one-year survival rates from the 24 trials from which data could be obtained are summarised in Table 3. When odds ratios were determined, XP was numerically better than all comparator regimens but one (BTC), with no significant between-regimen differences observed (Figure 4). The estimated 1-year survival rate varied from 23.2% (95% CI: 9.76% to 43.79%) for VC to 37.9% [95% CI: 23.30% to 57.62%]) for the regimen BTC; the 1-year survival rate for XP was 35.5% (95% CI: 22.58% to 50.00%).

Sensitivity analyses

Results of sensitivity analyses show that one-year survival rates varied little between adjusted and primary findings.

Overall response rate

Data for overall response rate were available from all 27 trials (Table 3). Analysis showed that the median overall response rate with XP was 29.8% (Table 4). The highest overall response rates were seen with BTC and bevacizumab + gemcitabine + cisplatin (BGP) (>40%), although most regimens had rates of between 20% and 30% (Table 4). Odds ratios for response generally favoured XP but some statistically significant between-regimen differences were detected. The odds ratio for BTC was superior to that of XP, whereas XP had a superior odds ratio when compared with vinorelbine + carboplatin (VC) and gemcitabine + carboplatin (GC) (Figure 5).

Sensitivity analyses

Results of sensitivity analyses show that overall response rates varied little between

adjusted and primary findings.

Toxicity

Toxicity data were reported inconsistently in the 27 trials evaluated, and varied greatly within and between treatment regimens. Therefore estimates of the incidences of the toxicity measures under consideration had large confidence intervals and are likely to be imprecise.

The expected rates of febrile neutropenia (derived from 18 studies) and neutropenia (derived from 26 studies), as estimated by the model, were lower with XP than with all comparators, although the only statistical difference was for neutropenia versus VP (Table 5). Thus, odds ratios for the risk of both febrile and severe neutropenia with XP versus comparator regimens all favoured XP, although, again, only comparisons versus VP were statistically significant (data not shown).

When nausea/vomiting rates were derived from the 24 studies that provided these data, the only comparison to favour XP was that versus BGP (not significant), whereas TC and VC induced significantly lower nausea/vomiting rates than XP (as shown by 95% CI). Rates of nausea/vomiting ranged from 1.03% (VC) to 33.2% (BGP), with XP having the second highest rate (13%) as most rates were reported to be <10%.

Rates of thrombocytopenia were derived from all 27 studies and ranged from 0.8% with paclitaxel 3-hour infusion + cisplatin (TP(3)) to 42.8% with GC (Table 5). Significant differences between regimens were observed for XP versus GC (favouring XP), GP (favouring XP), TP(3) (favouring TP(3)), VP (favouring VP) and docetaxel + cisplatin (DP; favouring DP). Odds ratios for thrombocytopenia risk showed similar findings (data not shown). The rate of anaemia with XP was 6.4%, a value similar to that of most comparator regimens (Table 5; rates were derived from 24 studies). No significant differences between treatments for rates or odds ratios (data not shown) for anaemia were observed.

Rates and odds ratios for diarrhoea for XP versus comparators did not differ significantly, with expected rates being 0% for all regimens. However, results for this analysis were derived from only 13 studies and were unstable, indicating that the model poorly fitted the data and had poor predictive potential.

Sensitivity analyses

Results of sensitivity analyses show that the toxicity findings varied little between adjusted and primary analyses.

Discussion

Word count: 1335

We performed an indirect comparison using a mixed treatment comparison model to compare XP with a number of alternative regimens used in the first-line treatment of advanced NSCLC. Our results indicate that XP does not differ significantly from other first-line regimens used in the treatment of NSCLC. Sensitivity analyses support this finding. This efficacy of XP relative to alternative regimens is further supported by results of analysis of the additional efficacy criteria TTP, 1-year survival rate and overall response rate. Overall, these analyses, and their respective sensitivity analyses, showed that in general, the efficacy of XP did not differ from that of its comparators.

Health authorities are interested in comparing a new treatment to several alternatives. When no randomised controlled trials are available, comparing a new treatment with alternative regimens poses a methodological challenge. The historical approach of extracting data from arms of different clinical trials and making comparisons using a Markov model leads to inaccuracy in results and is increasingly being recognised as inappropriate, as it takes for granted that the populations in the trials are comparable (Drummond & Sculpher 2005). Indirect comparisons are now considered more appropriate for comparing these data (Song et al. 2000, 2003). There are several methods that can be used depending on the characteristics of the information available (Glenny et al. 2005). In general, the methods for indirect comparisons are built on existing methods for meta-analyses that prevent the loss of randomisation by using adjustment and inclusion of a between-studies-differences parameter in the modelling. Indirect comparisons methods add a way to build bridges between studies by using the relative effect of a drug instead of the absolute effect. This allows a network of evidence to be formed linking many drugs by way of complex evidence structures.

Firm conclusions cannot be drawn concerning the relative benefits of XP compared with alternative treatments. Confidence intervals for TTP and 1-year survival analyses were wide showing that uncertainty of results exists for many comparisons. This is partially a result of the small number of data sources for many regimens and the wide range of patient numbers included in each study. Additionally, PFS and TTP were considered to provide equivalent information, which could have introduced bias. The two endpoints are not clinically the same, and this may have affected to ability of the algorithm to fit the data correctly, thus reducing precision. However, we considered it acceptable to combine these endpoints as relative differences not absolute differences were being analysed.

When toxicity was considered, XP tended to be associated with less severe neutropenia or febrile neutropenia than comparator regimens. VP was inferior to XP for risk of severe neutropenia, although this finding may have been driven by the results of only one study (Wozniak et al. 1998). Confirmation of this finding is therefore required. Confidence intervals were wide for febrile neutropenia, and no causal interpretation could be drawn. The risk of other toxicities (thrombocytopenia, anaemia, diarrhoea and nausea/vomiting) generally did not favour XP, although thrombocytopenia and nausea/vomiting were the only adverse events for which XP was less favourable than most comparators. The toxicity findings should, however, be viewed with caution, as rates observed throughout the various trials were quite heterogeneous. This would affect the robustness of our findings and is reflected by the wide confidence intervals obtained. Thus, until proven otherwise, XP and its comparators should be considered to be associated with similar risk of these events. It is worth noting that some studies allowed granulocyte-colony stimulating factors and/or medication to control nausea while others did not. This has not been considered in the analyses, but it is likely that there was little difference in usage between the various regimens. Additionally, use of

supportive care and duration of chemotherapy were not considered, and analyses did not consider the different scales and versions used across studies.

A total of 27 articles that fulfilled the chosen inclusion and exclusion criteria were included in this analysis. They enabled us to generate a network linking 19 drug regimens through indirect comparison. Study quality was homogeneous with the exception of the study by Manegold et al. (2007), for which data are available only within an abstract, and data were obtained from 13,064 patients who received first-line chemotherapy for NSCLC. The study of Manegold et al. (2007) was included as it provided the only available data for the BGP triplet combination. Hazard ratios were used to determine the relative effects of each treatment on overall survival using the methods described by Griffin et al. (2006), as median survival data are not appropriate for meta-analysis and result in biased, largely over- or under-estimated real treatment effects and loss of statistical power (Michiels et al. 2005; Duchateau et al. 2001). Time to progression was also analysed using hazard ratios for the same reasons. The methods used for this analysis were reviewed by an external statistician who provided positive feedback.

This analysis has limitations, the main one being adherence to the underlying exchangeability hypothesis of the model. Using a full Bayesian model enabled us to relax the hypothesis from “a treatment has the same effect in the various trials in which it was studied” to “a treatment effect can be characterised by the distribution fully described by the effects observed in the various trials which implemented the treatment”. Other limitations include standard confounding bias due to differences between trials not being due to treatment effect. Although sensitivity analyses were implemented to account for these biases, it was not possible to remove the possibility of confounding due to differences in the variability of the estimates in the trials. Adjusted sensitivity analyses also have some limitations: adjusting a model when few data are available can lead to convergence problems in algorithms. Consequently, any

conclusions have to consider that the primary analysis takes into account all the available information but disregards possible confounders which are a source of bias, and that the sensitivity analyses, which avoid these biases, can have low power when performed on few data. Limitations, not with standing, the sensitivity analyses generally supported the findings of their respective primary analyses. In addition, some regimens were better represented than others. For example, data concerning GP were available from 11 publications, whereas data for XP, VC, DC, GT, GV-VI, IP and BGP were available from only 1 study each. As the studies included in the analysis were conducted over a number of years, various methods were used for measuring drug benefit and toxicity. Hence, the response characterization and TTP have also several definitions. So as not to lose information, some assumptions were made that should be considered when interpreting these results (see methods section).

Despite precise inclusion and exclusion criteria, there were differences between the studies selected with respect to patient characteristics (particularly in terms of severity of disease and histology), study setting and the period during which the study was performed (which may have resulted in differences in the management and standard of care of cancer patients between studies). In addition, the percentage of PS=2 patients varied from 0 up to 59.5%, with the majority of studies including a small number of these patients. Recent recommendations are to exclude these patients from clinical trials. Similarly, the percentage of patients with a squamous histology varied from 0% to 55.64%, the average being 26.5%. Although the prognostic and predictive role of histology is only emerging, this finding has the potential to affect results since the presence/absence of squamous histology could affect the relative efficacies of XP and comparators. Neither pemetrexed nor bevacizumab is indicated for patients with squamous cell lung cancer. However, BTC has generally been evaluated only in patients with nonsquamous NSCLC because of poor tolerability in patients with squamous histology (Socinski 2008), whereas trials of XP have included patients with

squamous cell lung cancer. Our model was unable to address these differences because of limitations imposed by published data for other regimens. Additionally, our analyses were performed before the NSCLC indication for XP was limited to patients with non-squamous disease. Although the broader indication assessed in these analyses limits applicability to current treatment strategies, our results provide a framework for future modelling studies including economic evaluations.

In conclusion, these analyses find no evidence that pemetrexed, in a regimen containing cisplatin, differs significantly in terms of efficacy and tolerability from other chemotherapy regimens in the first-line treatment of advanced NSCLC. When considered with the results of other studies, XP can therefore be considered among the suitable first-line regimens for the treatment of patients with advanced non-squamous NSCLC.

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Figure Legends

Figure 1 Network of evidence (for abbreviations see table 1)

Figure 2 Estimated overall survival hazard ratios and corresponding 95% confidence intervals for comparator versus pemetrexed + cisplatin as the reference treatment (abbreviations for treatment regimens are defined in Table 1). XP was the reference treatment (denominator) and hazard ratios were computed using a mortality endpoint. Therefore a hazard ratio of 1 indicates that the overall survival hazard ratio with XP equals that of the comparator, a hazard ratio >1 indicates the overall survival hazard ratio favours XP, and a hazard ratio <1 indicates the overall survival hazard ratio favours the comparator

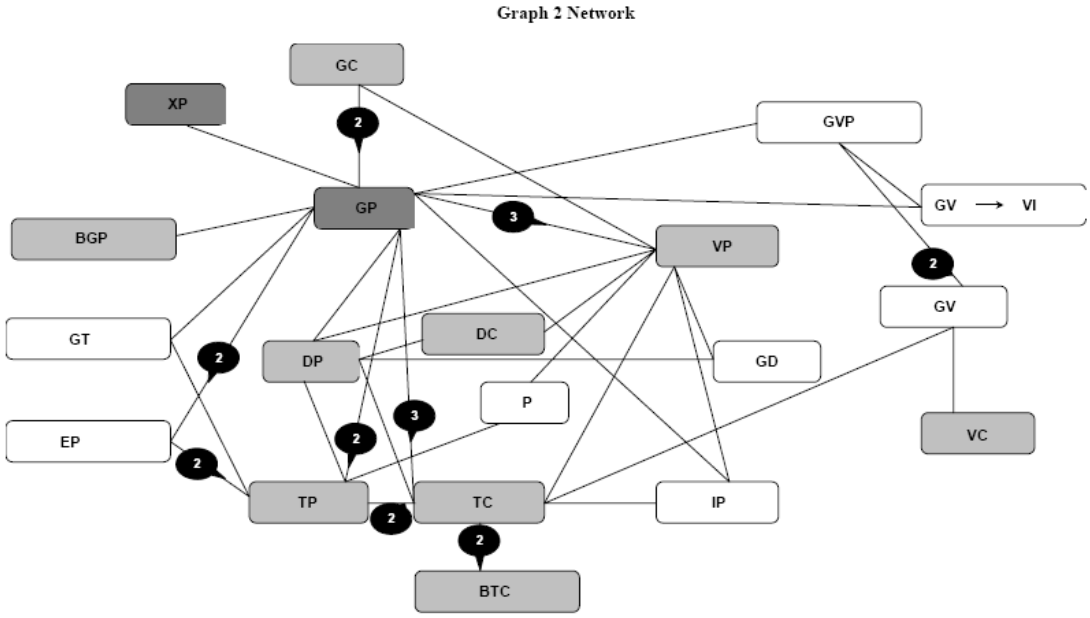
Figure 3 Estimated hazard ratios for progression of disease and corresponding 95% confidence intervals for comparator versus pemetrexed + cisplatin (abbreviations for treatment regimens are defined in Table 1). XP was the reference treatment (denominator) and hazard ratios were computed using a mortality endpoint. Therefore a hazard ratio of 1 indicates that the progression of disease hazard ratio with XP equals that of the comparator, a hazard ratio >1 indicates the progression of disease hazard ratio favours XP, and a hazard ratio <1 indicates the progression of disease hazard ratio favours the comparator

Figure 4 Estimated odds ratios for one-year survival rate and corresponding 95% confidence intervals for comparator versus pemetrexed + cisplatin (abbreviations for treatment regimens are defined in Table 1). XP was the reference treatment (denominator) and odds ratios were computed using a survival endpoint. Therefore an odds ratio of 1 indicates that the one-year

survival odds ratio with XP equals that of the comparator, an odds ratio <1 indicates one-year survival odds ratio favours XP, and an odds ratio >1 indicates one-year survival odds ratio favours the comparator

Figure 5 Estimated odds ratios for overall response rate and corresponding 95% confidence intervals for comparator versus pemetrexed + cisplatin (abbreviations for treatment regimens are defined in Table 1). XP was the reference treatment (denominator) and odds ratios were computed using a survival endpoint. Therefore an odds ratio of 1 indicates that the overall response rate odds ratio with XP equals that of the comparator, an odds ratio <1 indicates overall response rate odds ratio favours XP, and an odds ratio >1 indicates overall response rate odds ratio favours the comparator

Figure 1 Network of evidence (for abbreviations see table 1).



Definitions:

The plain line indicates that a direct comparison exist between the two products.

The plain line with a bubble indicates that X direct comparisons exist between the two products.

XX Dark grey zones are for the trial that includes pemetrexed

XX Light grey zones are for the trials that include a comparator which is of particular interest.

XX White zones are for the trials with comparators that are not of interest although they provide indirect evidence which are useful for the network.

Figure 2 Estimated overall survival hazard ratios and corresponding 95% confidence intervals for comparator versus pemetrexed + cisplatin as the reference treatment (abbreviations for treatment regimens are defined in Table 1). XP was the reference treatment (denominator) and hazard ratios were computed using a mortality endpoint. Therefore a hazard ratio of 1 indicates that the overall survival hazard ratio with XP equals that of the comparator, a hazard ratio >1 indicates the overall survival hazard ratio favours XP, and a hazard ratio <1 indicates the overall survival hazard ratio favours the comparator.

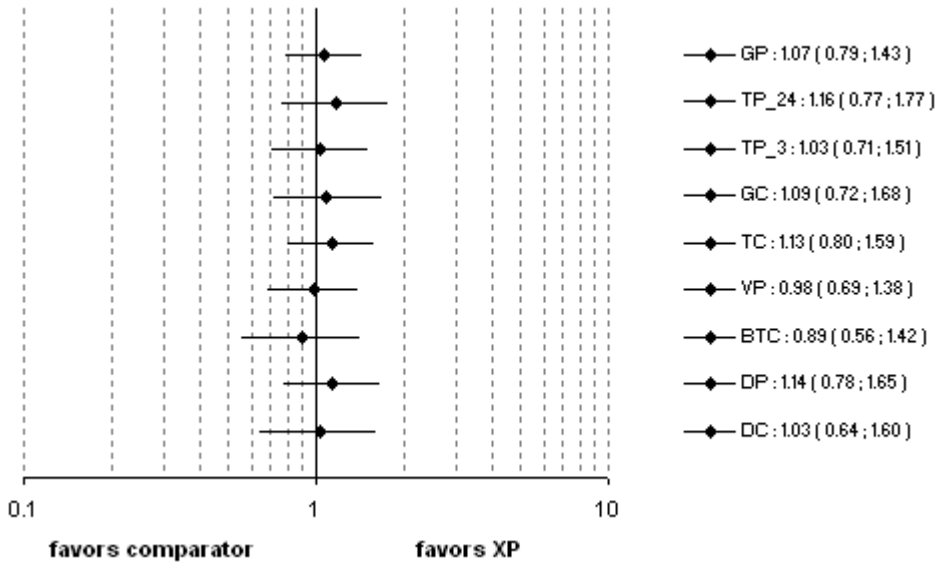


Figure 3 Estimated hazard ratios for progression of disease and corresponding 95% confidence intervals for comparator versus pemetrexed + cisplatin (abbreviations for treatment regimens are defined in Table 1). XP was the reference treatment (denominator) and hazard ratios were computed using a mortality endpoint. Therefore a hazard ratio of 1 indicates that the progression of disease hazard ratio with XP equals that of the comparator, a hazard ratio >1 indicates the progression of disease hazard ratio favours XP, and a hazard ratio <1 indicates the progression of disease hazard ratio favours the comparator.

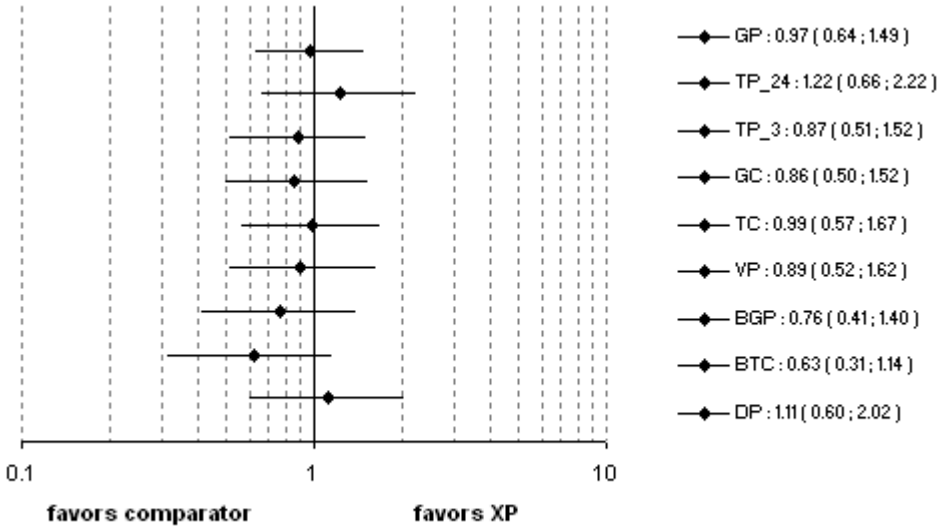


Figure 4 Estimated odds ratios for one-year survival rate and corresponding 95% confidence intervals for comparator versus pemetrexed + cisplatin (abbreviations for treatment regimens are defined in Table 1). XP was the reference treatment (denominator) and odds ratios were computed using a survival endpoint. Therefore an odds ratio of 1 indicates that the one-year survival odds ratio with XP equals that of the comparator, an odds ratio <1 indicates one-year survival odds ratio favours XP, and an odds ratio >1 indicates one-year survival odds ratio favours the comparator.

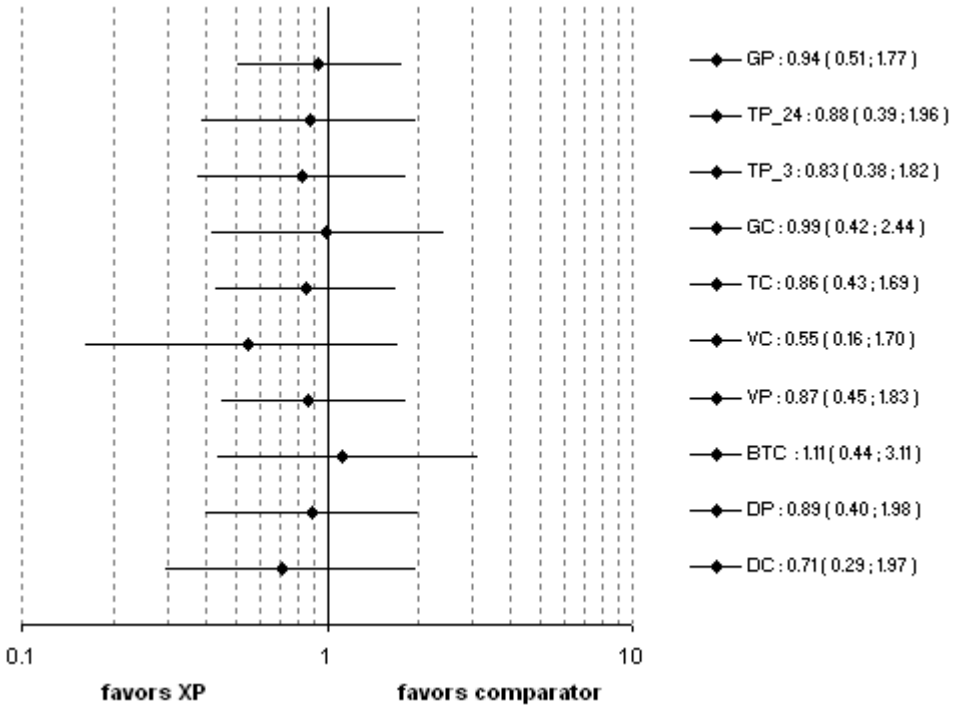


Figure 5 Estimated odds ratios for overall response rate and corresponding 95% confidence intervals for comparator versus pemetrexed + cisplatin (abbreviations for treatment regimens are defined in Table 1). XP was the reference treatment (denominator) and odds ratios were computed using a survival endpoint. Therefore an odds ratio of 1 indicates that the overall response rate odds ratio with XP equals that of the comparator, an odds ratio <1 indicates overall response rate odds ratio favours XP, and an odds ratio >1 indicates overall response rate odds ratio favours the comparator.

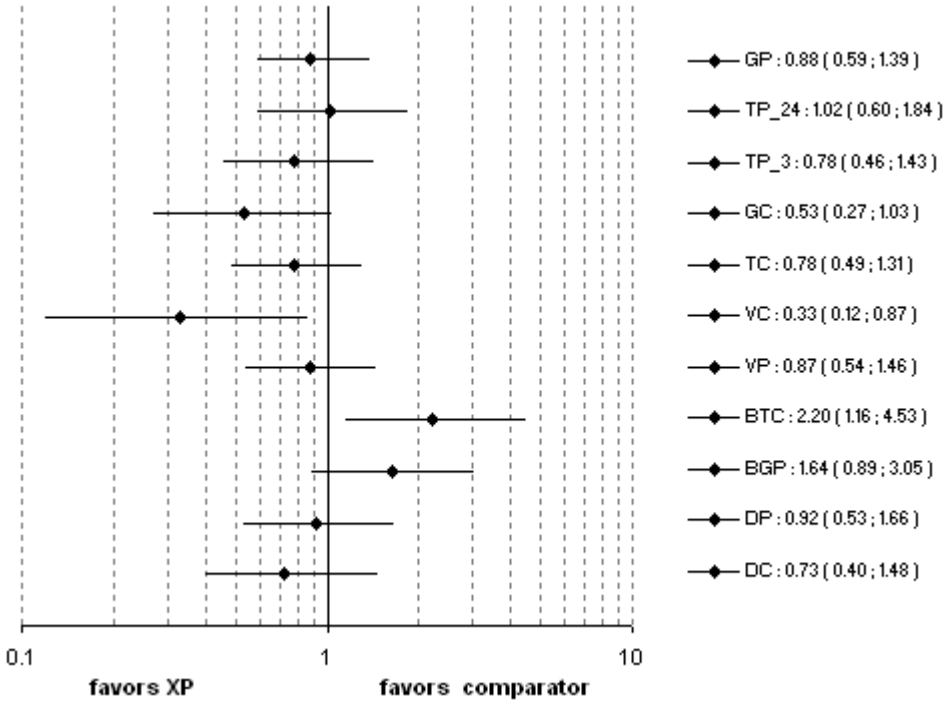


Table 1 Treatment regimens considered in analysis

Abbreviation	Treatment regimen
GP	gemcitabine + cisplatin
XP	pemetrexed + cisplatin
GVP	gemcitabine + vinorelbine + cisplatin
GV-VI	gemcitabine + vinorelbine followed with vinorelbine + ifosfamide
EP	etoposide + cisplatin
TP(24)	paclitaxel 24-hour infusion + cisplatin
TP(3)	paclitaxel 3-hour infusion + cisplatin
GC	gemcitabine + carboplatin
TC	paclitaxel + carboplatin
GV	gemcitabine + vinorelbine
P	cisplatin
VC	vinorelbine + carboplatin
GT	gemcitabine + paclitaxel
VP	vinorelbine + cisplatin
BTC	bevacizumab + paclitaxel + carboplatin
BGP	bevacizumab + gemcitabine + cisplatin
IP	irinotecan + cisplatin
GD	gemcitabine + docetaxel
DP	docetaxel + cisplatin
DC	docetaxel + carboplatin

Table 2 Studies included in analysis and patient characteristics for each study

Study	Publication year	No. of patients	Median age (years)	Male (%)	PS2 (%)	Stage IV disease (%)	Squamous histology (%)	Adeno-carcinoma or large cell histology (%)	Treatment regimens	Study quality[d] (%)
Scagliotti	2008	1,725	61.0	70.1	0.0	75.9	27.4	72.6	GP, XP	86.4
Alberola	2003	557	59.3	87.7	16.5	79.2	24.2	26.2	GP, GVP, GV-VI	67.0
Belani	2005	369	61.0	61.2	0.0	78.0	NR	NR	EP, TC	69.3
Bonomi	2000	574	61.7	63.7	0.0	80.7	NR	NR	EP, TP(24)	55.7
Cardenal	1999	133	58.5	92.6	14.8	50.4	45.2	44.5	GP, EP	69.3
Esteban	2006	114	59.5	82.5	59.5	92.5	35.5	51.5	GVP, GV	63.6
Fossella	2003	1,218	60.3	73.0	3.9	67.2	33.5	53.5	VP, DP, DC	68.2
Gatzemeier	2000	414	60.0	80.5	18.0	70.0	35.5	57.0	TP(3), P	75.0
Gebbia	2003	278	61.5	77.0	18.0	53.5	52.0	35.0	GP, VP	62.5
Johnson	2004	98	NR	62.9	6.7	84.9	20.5	70.6	TC, BTC	59.1
Katakami	2006	131	63.0	65.6	0.0	74.1	27.6	66.4	GD, DP	72.7
Kelly	2001	408	61.5	68.5	0.0	88.5	NR	NR	TC, VP	70.5
Laack	2004	214	61.0	75.0	16.0	87.0	32.0	58.0	GVP, GV	76.1
Lilenbaum	2005	165	64.5	56.5	14.5	81.5	NR	NR	TC, GV	68.2
Manegold	2007	1,037	58.3	63.7	0.0	77.3	0.0	NR	GP, BGP	17.0
Mazzanti	2003	120	63.0	78.3	17.5	60.0	28.3	49.2	GP, GC	86.4
Ohe	2007	581	61.8	68.5	0.0	80.3	18.1	76.1	GP, TC, VP, IP	73.9
Pujol	2005	311	58.5	79.8	8.0	82.3	27.7	71.7	VP, GD	86.4

Rosell	2002	618	58.0	82.5	17.3	60.0	37.5	55.5	TP(3), TC	83.0
Sandler	2006	773	NA	54.1	0.0	76.0	0.0	93.5	TC, BTC	79.5
Scagliotti	2002	607	62.7	78.4	7.3	81.3	30.7	58.3	GP, TC, VP	76.1
Schiller	2002	1,155	63.0	62.8	5.5	86.8	NR	NR	GP, TP(24), TC, DP	72.7
Smit	2003	458	56.7	66.2	11.7	80.9	22.1	74.6	GP, TP(3), GT	80.7
Tan	2005	316	59.5	75.3	0.0	79.9	32.9	42.7	GV, VC	75.0
Thomas	2006	99	58.1	83.0	13.0	91.0	42.9	57.1	GC, VP	70.5
Wozniak	1998	415	63.0	67.5	0.0	92.0	21.0	66.5	P, VP	63.6
Zatloukal	2003	176	62.5	76.5	NA	60.5	50.9	36.5	GP, GC	72.7
		13064[b]	56.6[c]	70.3[c]	5.7[c]	71.8[c]	20.1[c]	45.3[c]		58.3[c]

a Median
b Total number of patients receiving treatment arms of interest in all studies
c Weighted average (the weight being the number of patients).
d Maximum possible score from the ELCWP scale is 88 (=100%). Only percentage values are reported.
NR = Data not available; PS = performance status.

Table 3 Hazard ratios for overall survival and time to progression, and one-year survival and tumour response rates by individual study

Study	Treatment regimens[a]	Hazard ratio[a]		Rate	
		Overall survival	Time to progression	Response (% of patients)	One-year survival (% of patients)
Scagliotti 2008	GP, XP	0.94	1.03[b]	28, 31	42, 44
Alberola	GP, GVP, GV-VI	NR	NR	42, 41, 27	38, 33, 34
Belani	EP, TC	NR	NR	15, 23	37, 32
Bonomi	EP, TP(24)	NR	NR	12, 27	32, 39
Cardenal	GP, EP	0.77[b]	0.8[b]	41, 22	32, 26
Esteban	GVP, GV	NR	NR	47, 37	28, 26
Fossella	VP, DP	1.18	NR	25, 32	40, 46
	VP, DC	1.05	NR	25, 24	40, 38
Gatzemeier	TP(3), P	0.98	1.25[c]	24,16	30, 36
Gebbia	GP, VP	NR	NR	34, 44	20, 24
Johnson	TC, BTC	NR	1.83[c]	19, 30	NR
Katakami	GD, DP	0.82	NR	27, 24	57, 48
Kelly	TC, VP	1.02[c]	NR	25, 28	38, 36
Laack	GVP, GV	1.05[c]	1.13[cd]	28, 13	28, 34
Lilenbaum	TC, GV	NR	NR	17, 15	32, 38
Manegold	GP, BGP	NR	0.82	20, 32	NR
Mazzanti	GP, GC	1.09[c]	1.06[c]	42, 31	43, 43
Ohe	GP, IP	0.99	NR	30, 31	60, 59
	TC, IP	1.11	NR	32, 31	51, 59
	VP, IP	1.17	NR	33, 31	48, 59
Pujol	VP, GD	0.90	1.04[bd]	36, 31	42, 46
Rosell	TP(3), TC	1.22	1.19[c]	26, 23	38, 33

Study	Treatment regimens[a]	Hazard ratio[a]		Rate	
		Overall survival	Time to progression	Response (% of patients)	One-year survival (% of patients)
Sandler	TC, BTC	0.79	0.66[bd]	15, 35	44, 51
Scagliotti 2002	GP, VP	0.92	1.1	30, 30	37, 37
	TC, VP	0.87	0.96	32, 30	43, 37
Schiller	GP, DP	0.94[b]	0.87[b]	22, 17	36, 31
	GP, TP(24)	0.92[b]	0.79[b]	22, 21	36, 31
	GP, TC	0.96[b]	0.84[b]	22, 17	36, 34
Smit	GP, TP(3)	1.05[c]	1.05[cd]	37, 32	33, 36
	GT, TP(3)	1.21[c]	1.19[cd]	28, 32	27, 36
Tan	GV, VC	1.40[c]	NR	28, 21	49, 34
Thomas	GC, VP	NR	NR	20, 29	NR
Wozniak	P, VP	1.40[c]	1.47[cd]	12, 26	20, 36
Zatloukal	GP, GC	1.02[c]	1.3[c]	41, 29	33, 36

a Hazard ratio is for underlined treatment regimen. Treatment abbreviations are defined in Table 1

b Value obtained from the meta-analysis of Le Chevalier (2005); data not available from published study

c Value calculated using the Parmar method (Parmar et al); data not available from published study

d Progression-free survival

NR = not reported.

Table 4 Overall response rate as determined for the mixed treatment comparison model

Treatment regimen[a]	Median (% of patients)	95% Confidence interval
XP	**29.8**	**20.7- 38.5**
TP(24)	30.3	22.7 - 38.9
TP(3)	24.7	18.4 - 32.3
BTC	48.7	35.5 - 61.4
BGP	41.2	30.5 - 53.6
DP	28.2	21.2 - 36.2
VP	27.1	22.0 - 32.5
GP	27.3	24.7 - 30.3
TC	25.1	20.1 - 30.0
DC	23.8	16.5 - 34.0
GC	18.4	12.3 - 26.3
VC	12.3	5.5 - 25.8
SD	0.1	0.0 - 0.4

a Abbreviations for treatment regimens are defined in Table 1.

Table 5 Median (95% confidence interval) expected rate of haematological toxicities by regimen

Treatment regimen[a]	Febrile neutropenia	Grade 3/4 neutropenia	Grade 3/4 thrombocytopenia	Grade 3/4 anaemia
XP	**1.03 (0.04-17.95)b**	**20.47 (7.53-45.67)**	**8.32 (2.44-26.50)**	**6.38 (2.58-15.16)**
GP	3.07 (2.08-4.26)	34.67 (31.37-38.08)	23.82 (21.08-26.76)	11.02 (9.33-12.86)
TP(24)	13.66 (1.28-65.45)	53.25 (28.95-77.24)	2.35 (1.02-5.99)	4.18 (2.20-8.00)
TP(3)	0.60 (0.05-5.44)	27.39 (12.77-47.25)	0.78 (0.25-2.11)	4.66 (2.16-8.83)
DP	8.91 (1.06-48.01)	46.84 (27.09-67.66)	1.17 (0.41-2.71)	4.49 (2.39-8.26)
VP	12.30 (2.15-47.71)	62.98 (49.53-75.78)	1.85 (0.91-3.44)	10.62 (6.85-15.29)
TC	3.99 (0.86-17.86)	44.43 (31.05-58.91)	4.87 (2.87-8.48)	4.47 (2.84-6.91)
DC	8.70 (0.33-68.73)	51.14 (22.69-79.63)	3.36 (0.88-10.11)	5.31 (2.24-13.09)
GC	1.55 (0.01-47.66)	30.36 (16.20-50.07)	42.81 (23.46-65.89)	15.18 (8.20-28.26)
VC	85.69 (3.99-99.95)	45.77 (12.52-82.30)	6.57% (0.68-51.39)	16.95 (3.39-53.63)

a Abbreviations for treatment regimens are defined in Table 1.

Appendix 1. Selection tree for papers identified from MEDLINE searches