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Optimal duration of first-line chemotherapy for advanced non-small cell lung cancer: A systematic review with meta-analysis

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ABSTRACT

Background: The optimal duration of first-line chemotherapy for advanced non-small cell lung cancer (NSCLC) has been a matter for debate for nearly 20 years. In order to elucidate this issue, a meta-analysis comparing the different durations of same treatments was performed.

Methods: We searched for all published randomised controlled trials (RCTs) comparing different durations of first-line treatment of advanced NSCLC. The MEDLINE, EMBASE, LILACS and CENTRAL databases were searched for RCTs comparing a defined number of cycles of chemotherapy versus continuing treatment until disease progression, or a defined number of cycles versus a higher number of cycles of the same chemotherapy. Trials including biological agents were excluded.

Results: Seven trials that included 1559 patients were analysed. Treatment for more than 4 cycles was associated with a non-statistically significant decrease in the hazard of mortality relative to shorter treatment (hazard ratio (HR) = 0.97; 95% confidence interval (CI) = 0.84–1.11; $P = .65$). In those treated with third-generation chemotherapy through the whole study time, treatment for more than 4 cycles was associated with a non-statistically significant increase in mortality (HR = 1.08; 95% CI = 0.90–1.28; $P = .28$). Patients receiving more chemotherapy had significant longer progression-free survival (HR = .75; 95% CI = 0.60–0.85; $P < 0.0001$) than the group with shorter duration of treatment. In an intent-to-treat analysis, there was no difference in the overall response rate between the groups (odds ratio (OR) = 0.78; 95% CI = 0.60–1.01; $P = .96$). Longer treatment was associated with more severe leucopaenia but with no significant increase in non-haematological toxicities.

Conclusions: In patients with advanced NSCLC the use of more than 4 cycles of first-line chemotherapy with third-generation regimens significantly increases progression-free survival but not overall survival and is associated with higher incidence of adverse events. There is no evidence to support continuous chemotherapy until progression in patients with lung cancer.

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1. Introduction

Lung cancer is the third most common cancer and the leading cause of cancer related death worldwide.[1] About 87% of these tumours are non-small cell histological types (NSCLC).[2] Most of patients present incurable disease at the time of diagnosis and even those patients suitable for curative treatment have a high rate of relapse,[3] resulting in a 5-year survival rate of 15%.[4] Therefore, the majority of patients are considered potential candidates to receive systemic treatment.

Recently, the wide spectrum of regimens has been added to the clinical practice, making the precise integration of potential benefits even more challenging. In patients with advanced disease, palliative chemotherapy increases overall survival and quality of life when compared to supportive care as stated in a meta-analysis.[5] The development of new platinum-based doublets, known as third-generation regimens, had shown to improve survival,[6] and the addition of effective second[7–9] and third-line[10] treatments brought more variables to the management of advanced NSCLC.

Although continuous first-line treatment until progression – a general rule in all other solid tumours – has been associated with a higher response rate in lung cancer, the maintenance of chemotherapy during stable disease may potentially expose patients to additional toxicity without offering extra gains. It may also postpone the use of other antitumour agents and prevent patients from derived benefits of these treatments. Several randomised controlled trials evaluated the role of continuous or extended chemotherapy in patients with advanced NSCLC.[11–14] Most of them found significant longer time to progression but without benefits in overall survival.

Despite the modest results of these trials, a recent meta-analysis suggested that higher response rates may be a surrogate of increase in overall survival and time to progression in patients treated with first-line chemotherapy.[15] This review hypothesised that samples larger than those regularly found in lung cancer trials would be needed to identify these relevant correlations. Considering that actual regimens are more active, the prolongation of treatment may have an impact on overall survival not yet shown due to sample size inadequacy.

Facing this conflicting scenario, we undertook this systematic review with meta-analysis of the published data from randomised trials that assessed different durations of first-line chemotherapy for lung cancer. The main goal was to address a controversial clinical question: is overall survival improved with prolonged first-line chemotherapy when compared with limited duration of treatment?

2. Methods

2.1. Search strategy

Studies published between January 1973 and December 2007 were identified through searches in the following electronic databases: MEDLINE, EMBASE, LILACS and CENTRAL. There were no language restrictions. We used a wide search strategy, through words linked to lung cancer (lung OR pulmonar* AND tumour OR neoplasm OR carcinoma OR cancer), chemotherapy (drug therapy OR chemotherap*) and randomised trials (random*) in all fields.

We hand-searched the reference lists of related reviews for additional publications. All references of relevant articles were scanned and all additional studies of potential interest were retrieved for further analysis.

2.2. Selection criteria

We sought to identify all the published randomised controlled clinical trials with a parallel design comparing the same chemotherapy scheme, or at least some of the original drugs used, in different durations as first-line treatment for advanced NSCLC. Trials that included target drugs were excluded. No limit of publication date was applied.

The original published articles of all located references were retrieved for a more detailed analysis. All published randomised controlled trials that included patients with histological proven NSCLC and with the evidence of cancer progression or advanced disease not amenable to curable treatment were included. No attempt to restrict the search according to methodological characteristics was made.

Two of the authors (J.P.L. and A.D.S.) reviewed the list of references and independently selected the studies. The final selection of the included studies was reached through a consensus meeting.

2.3. Data extraction

The name of the first author and the year of publication of the article were used for identification purposes. Data from all studies were extracted independently by two of the authors (J.P.L. and L.V.S.). When disagreements occurred, a third reviewer (A.D.S.) was consulted.

The main outcomes analysed were progression-free survival (PFS) and overall survival (OS). Other points of interest were response rates and grade 3/4 toxicities. When the published article did not present the needed data to determine PFS or OS, the authors were contacted to provide the pending information. Toxicity data were retrieved as available in the publication.

In trials that reported response of the assessable population rather than the intention-to-treat population, we adjusted the denominator to indicate the reported number of patients undergoing randomisation.

The hazard ratios (HRs) were directly extracted from the original study or were estimated indirectly using either the reported number of events and the corresponding *P* value for the log-rank statistics, or by reading off survival curves as suggested by Parmar and colleagues.[16] The calculations were carried out using a spreadsheet provided by Tierney and colleagues.[17] The original survival curves from electronic publication were enlarged, and data extraction was based on reading off electronic coordinates for each point of interest in order to decrease reading errors.

2.4. Statistical analysis and synthesis

Details regarding the main methodological dimensions empirically linked to bias as described by Deeks and colleagues[18] were extracted, and the methodological quality of each selected trial was assessed by two reviewers (J.P.L. and A.D.S.). Special attention was given to the generation and concealment of the sequence of randomisation, blinding, whether an intention-to-treat analysis (ITT) was performed or not, the use of placebo, and source of funding. These data were applied in a subgroup, and sensitivity analyses were performed to test the stability of our conclusions.

The RevMan 5.0 software (Cochrane Collaboration's Information Management System) was used to perform the meta-analysis. The effect of the treatment for each single study was expressed as a HR of the longer duration treatment arm over the shorter duration treatment arm. Thus, a HR greater than one favours the shorter duration arm, whereas a HR less than 1 favours the longer duration arm. The 95% confidence interval (CI) was calculated for each point estimate.

The results were calculated as HR, odds ratio (OR) or risk difference (RD) and are presented with the correspondent 95% CI. Statistical heterogeneity of the results of the trials was assessed by the test of chi-square (chi),[19] and was expressed as I^2 index, as described by Higgins and colleagues.[20] When heterogeneity was detected, a possible explanation for it was intensively pursued. If a reasonable cause was found, a separate analysis was then performed.

If the cause was not apparent and heterogeneity was caused by divergent data in terms of direction of results (i.e. data favouring one or other treatment), we chose not to pool the data.

3. Results

Nine potentially eligible trials, published between 1989 and 2007 were analysed.[11–14,21–25] One study was excluded because it included a different drug from the original regimen, configuring sequential therapy.[13] It was not possible to extract or obtain data from one study, in which all data presented were median survival,[14] information not feasible to pool for survival comparison.[26] The remaining seven trials,[11,12,21–25] comprising 1559 patients, had the data extracted from the publication or sent by the authors, and were included for meta-analysis. None of the selected trials was a placebo-controlled, double-blind trial. Details about methodological potentially linked to bias are described in Table 1.

Two studies were carried out in the United States (US), four in Europe and one in Asia. All trials were reported in the English language.

All trials tested platinum combinations except one.[12] Three trials[11,23,25] included the second randomisation after an initial period of identical treatment: two randomised for best supportive care (BSC) or a continuous single drug treatment[11,23] and one for additional cycles.[25] The description of post-progression treatment was scarce: just one trial clearly described therapy after first-line progression during the study.[22] Frequency of second-line therapy was similar between longer and shorter treatment arms in all trials but one,[25] in which it were more commonly offered to patients in the shorter arm. A detailed description of treatment arms of all included studies is presented in Table 2.

3.1. Overall survival

The impact of the duration of treatment on OS was estimated directly or indirectly for all trials, with 1559 patients. No single study demonstrated statistically significant results. After approximately 1050 deaths, there was no difference in OS between arms (HR 0.97; 95% CI 0.84–1.11; $P = 0.65$). There was no significant heterogeneity ($P = 0.60$; $I^2 = 0\%$) nor publication bias across trials (Fig. 1).

Alkylant-based chemotherapy has been shown to be deleterious when used for advanced NSCLC.[5] One of the included studies tested an alkylant-based therapy.[12] Therefore, the inclusion of such trial could dilute the benefits of platinum-based treatment. Performing the analysis with only platinum-based trials[11,21–25] (1485 patients) had no appreciable change in the results (HR 0.97; 95% CI 0.84–1.12; $P = 0.68$), with no heterogeneity between trials ($P = 0.48$; $I^2 = 0\%$) (data not shown).

Trials with third-generation platinum combinations during all treatment time could be theoretically considered the most active non-biological regimen. Clustering such trials[22,24,25] (841 patients, 647 deaths), the result was similar, with no differences between the groups (HR 1.08; 95% CI 0.90–1.28; $P = 0.41$), without heterogeneity ($P = 0.91$; $I^2 = 0\%$) (Fig. 2).

Table 1 – Characteristics of included studies.

Authors	Year	Random	Allocation	Withdrawn descript	Alpha error	Beta error	ITT	Placebo	Multi-centric	Sponsor
Park et al.[25]	2007	Adequate	Adequate	Yes	Yes	Yes	Yes	No	Yes	Academic
Plessen et al.[24]	2006	Adequate	Unclear	Yes	Yes	Yes	Yes	No	Yes	Both
Brodowicz et al.[23]	2006	Adequate	Unclear	Yes	Yes	Yes	Yes	No	Yes	Both
Belani et al.[11]	2003	Unclear	Unclear	Yes	No	Yes	No	No	Yes	Industry
Socinski et al.[22]	2002	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes	Industry
Smith et al.[21]	2001	Unclear	Unclear	No	No	No	Yes	No	Yes	Unclear
Buccheri et al.[12]	1989	Unclear	Unclear	No	No	No	Yes	Yes	No	Unclear

Abbreviations: ITT: intention-to-treat analysis; random: randomisation; both: pharmaceutical and academic sponsorship.

Table 2 – Description of treatments arms.

Authors	Duration of longer arm	Duration of shorter arm	Chemotherapy regimen
Park et al.[25] No. of patients	6 cycles (158)	4 cycles (156)	Cisplatin 70 mg/m^2 on D1 plus either a taxane (paclitaxel 175 mg/m^2 or docetaxel 75 mg/m^2) on D1 or gemcitabine 1000 mg/m^2 on D1 and D8 every 3 weeks
Plessen et al.[24] No. of patients	6 cycles (147)	3 cycles (150)	Carboplatin AUC 5 on D1 plus vinorelbine 25 mg/m^2 on D1 and D8 every 3 weeks
Brodowicz et al.[23] No. of patients[a]	Until progression (138)	4 cycles (68)	Cisplatin 80 mg/m^2 on D1 plus gemcitabine 1250 mg/m^2 on D1 and D8 every 3 weeks for a maximum of four cycles. Then, randomised to BSC or gemcitabine 1250 mg/m^2 on D 1 and D8 every 3 weeks
Belani et al.[11] No. of patients[b]	Until progression (65)	4 cycles (65)	Carboplatin plus paclitaxel for 4 months. Re-randomised to BSC or paclitaxel 70 mg/m^2 on D1, D8 and D15 every 4 weeks
Socinski et al.[22] No. of patients Smith et al.[21] No. of patients	Until progression (116) 6 cycles (153)	4 cycles (114) 3 cycles (155)	Carboplatin AUC 6 on D1 plus paclitaxel 200 mg/m^2 on D1 every 3 weeks. Second-line with paclitaxel 80 mg/m^2 weekly for both arms Mitomycin 8 mg/m^2 on D1 (given on courses 1, 2, 4, and 6) plus cisplatin 50 mg/m^2 on D1 plus vinblastine 6 mg/m^2 (maximum of 10 mg) on D1 plus every 3 weeks
Buccheri et al.[12] No. of patients[b]	Until progression (38)	3 cycles (36)	Methotrexate 40 mg/m^2 on D1 plus doxorubicin 40 mg/m^2 on D1 plus cyclophosphamide 400 mg/m^2 on D1 plus lomustine 30 mg/m^2 on D1 every 3 weeks[c]

Abbreviations: No. of patients: number of patients enrolled in each arm of study; AUC: area under the curve.
a,b Trials with second randomisation.
c Doxorubicin was omitted when the maximum cumulative dose was reached.

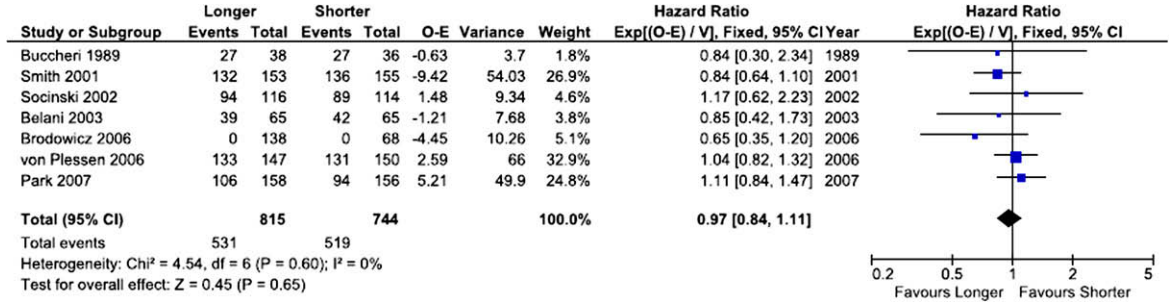

Fig. 1 – Meta-analysis of overall survival.

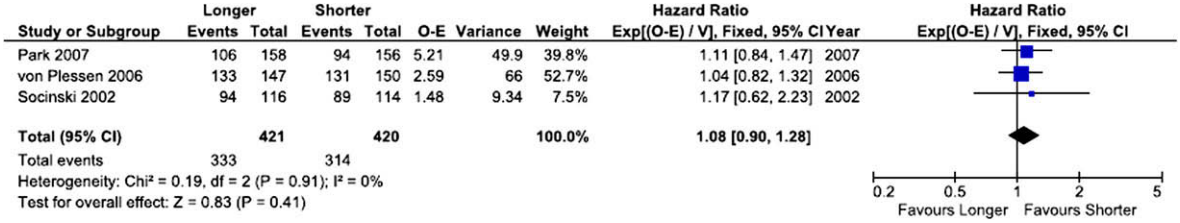

Fig. 2 – Meta-analysis of overall survival with third-generation doublets during all treatment time.

3.2. *Progression-free survival*

Information concerning PFS was available in all trials except one study.[22] Thus PFS analysis was based on data extracted from six trials and 1329 patients. The definition of progressive disease was based on WHO criteria in for trials[11,21,23,25] and in RECIST criteria in one.[24] Two studies presented statistically significant results favouring longer treatment.[23,25] The meta-analysis showed a significant increase in PFS in the longer arm (HR 0.75; 95% CI 0.65–0.85; $P < 0.0001$), with no heterogeneity between trials ($P = 0.23$; $I^2 = 28\%$) (Fig. 3). No publication bias was found by the funnel plot graphic model despite a wide range of variation (data not shown).

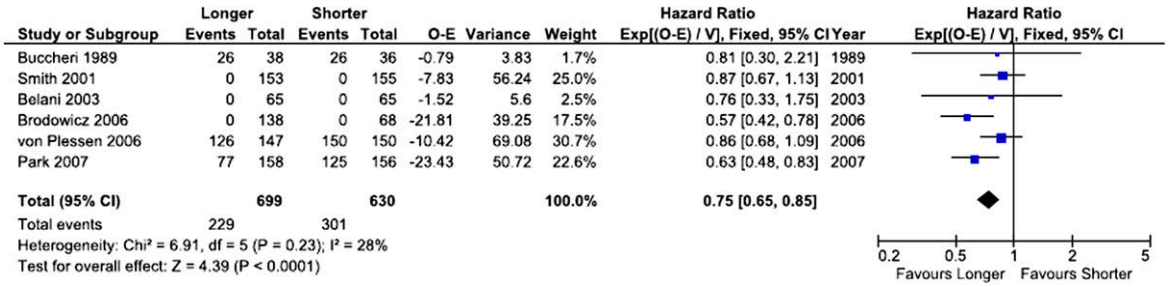

Fig. 3 – Meta-analysis of progression-free survival.

3.3. *Response rates*

Data for treatment response were reported in four trials, with 1059 patients included.[21–23,25] Considering only the evaluable population, overall RRs were similar among the groups (OR 0.78; 95% CI 0.60–1.01; $P = 0.06$) with no heterogeneity between trials ($P = 0.95$; $I^2 = 0\%$) (Fig. 4). Adjusting the denominator to the intention-to-treat analysis, there was absolutely no change in the results.

Data concerning time to response was available in just two trials, making analysis inadequate.

3.4. *Haematological toxicity*

Only five trials provided data on grade 3/4 haematological toxicity and therefore, it was feasible to compare the incidence of leucopaenia and neutropenia.[21–25] The meta-analysis showed a significant increase in haematological toxicity in the longer arm (OR 1.31; 95% CI 1.01–1.69; $P = 0.04$), however, with relevant heterogeneity between trials ($P = 0.16$; $I^2 = 40\%$). As previously planned, the possible causes of heterogeneity were explored to determine if it was appropriate to pool the trials. Only one trial described more events related to toxicity in the shorter arm, and it seemed to be responsible for the significant heterogeneity.[24] The authors described in the original article that the recording of toxicity was not systematic, what might compromised the validity of such data. By excluding this trial of the analysis, the meta-analysis shows that the incidence of haematological toxicities grade 3/4 were significant higher in patients of the longer arm (OR 1.55; 95% CI 1.14–2.10; $P = 0.005$), without significant heterogeneity ($P = 0.47$; $I^2 = 0\%$) (Fig. 5). The number needed to harm (NNH) was 13.

3.5. *Non-haematological toxicity*

Non-haematological toxicities were described in almost all studies, and the more frequent included nausea, vomiting, flu-like syndrome, asthenia, hypotension and fever. Data regarding grade 3/4 non-haematological toxicities were extractable in four studies.[21–23,25] After pooling in the meta-analysis, it revealed no statistical difference between groups (OR 1.06; 95% CI 0.66–1.68; $P = 0.82$) without heterogeneity ($P = 0.96$; $I^2 = 0\%$) (Fig. 6). These results must be treated with

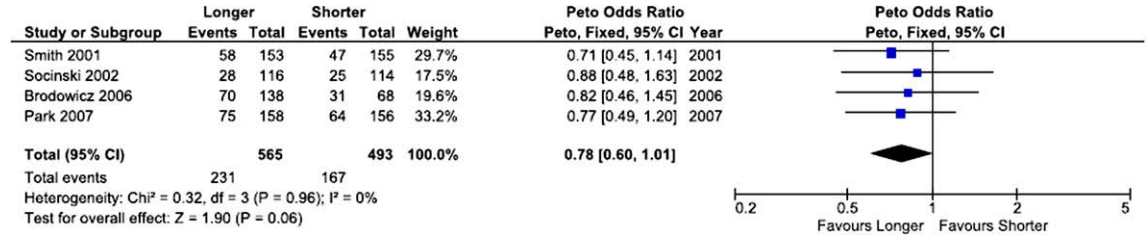

Fig. 4 – Meta-analysis of overall response rate in assessable population.

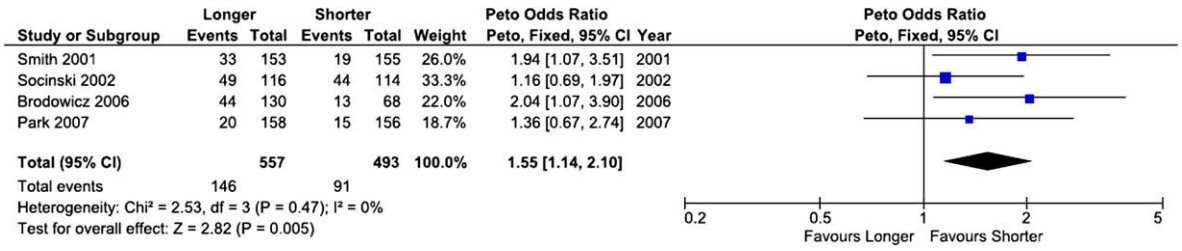

Fig. 5 – Meta-analysis of toxicity grade 3/4: neutropenia and leucopaenia.

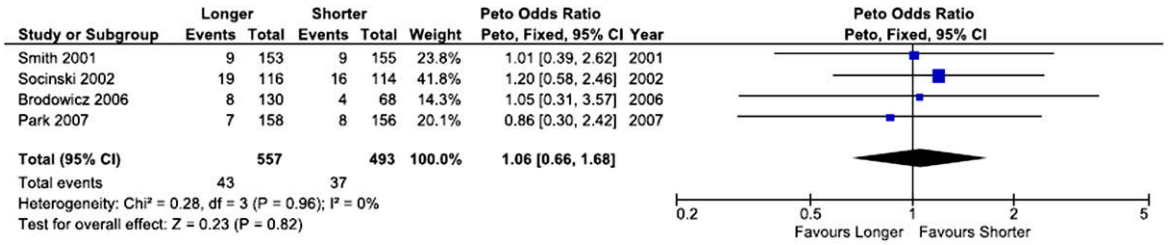

Fig. 6 – Meta-analysis of toxicity grade 3/4: nausea and vomiting.

caution, because of the difficulties in pooling data described in different ways. All trials described some non-haematological toxicity, but it was not feasible to extract and pool the data as provided in the publication.

4. Discussion

Given the incurable nature of the disease, the role of chemotherapy in metastatic NSCLC has been limited to prolong survival, palliate symptoms and provide better quality of life. Thus, the duration of chemotherapy administration – while it may interfere in some relevant endpoints – must be carefully balanced against its toxicities. Previous studies tested the hypothesis that the prolongation of chemotherapy could improve survival despite the risk of additional toxicity.[21,22] Although all randomised trials failed to prove gain in overall survival, some researchers advocated that new trials with bigger sample size would be necessary to prove the surrogacy of progression-free survival to overall survival. A meta-analysis of the previous publication could answer some of the questions, including if the prolonged treatment would really benefit the patients. This systematic review represents the best current evidence about the duration of chemotherapy in first-line treatment of advanced NSCLC.

As the result of this systematic review, we identified the trials with best methodological design to address this question. The majority of the included trials used platinum-based regimens, currently considered the most appropriate initial treatment for advanced NSCLC. Just one study evaluated continuous chemotherapy with methotrexate, doxorubicin, cyclophosphamide and lomustine (MACC regimen) – an alkylant-based treatment considered deleterious – with best supportive care.[12]

The main finding of this pooled analysis, with data obtained from more than 1500 NSCL patients, is that the prolongation of first-line therapy over three to 4 cycles does not translate into overall survival benefit. Differently, data concerning progression-free survival pointed to a different situation. Longer treatment yielded a larger progression-free survival, decreasing the risk of progression in 25%, with statistical significance and acceptable heterogeneity ($I^2 = 28\%$).

According to a recent meta-analysis, it was expected that increments in progression-free survival would cause modest but significant improvements in overall survival. However, only larger samples would allow to identify these differences.[15] The pooled sample achieved in this systematic review with more than 1300 patients would be enough to detect the surrogacy between progression-free survival and overall survival, but this did not occur. The absence of correlation between improvement in progression and overall survival in our study may be related to the low frequency (32%) in reporting progression times in the trials included in that meta-analysis.[15] This fact may potentially compromise the quantitative characteristics of correlation and ultimately make the assumption of dependence risky.

Similarly to progression-free survival in NSCLC, the response rate was also considered a potential surrogate endpoint of survival.[15] In this case, the trial size would not be a critical aspect but large differences in response rate would be necessary to predict a significant survival benefit. The response rate found in our meta-analysis was similar between different durations of treatment. Therefore, no correlation to survival can be applied.

Another aim of this analysis was to examine whether prolonged treatment was associated with increased toxicity. While neutropaenia and leucopaenia were statistically more frequent, nausea and vomiting were similar in both groups. Unfortunately, we could not analyse other important toxicities such as neuropathy or febrile neutropenia due to the paucity of data reported in the trials. The specific concern of increased neuropathy with prolonged use of neurotoxic drugs such as cisplatin and taxanes is worrisome. The quality of life of patients receiving shorter or longer treatments could not be assessed in our study because different and non-convertible questionnaires were used throughout the included studies.

Based on a meta-analysis of data obtained from seven studies, this review showed no evidence of a difference in overall survival to support the maintenance of the first-line chemotherapy until progression in patients with lung cancer.

The present study has the typical limitations of the meta-analytical methodology. Our findings and interpretations were limited by the quality and quantity of available evidence on the effects of prolonged treatment. Additionally, only published data were used in this meta-analysis. An analysis of individual patient data would be more powerful to confirm our findings. Another source of bias is related to the possible existence of some unpublished studies, which could lead to potential publication bias. We found no indication of such bias by using statistical methods designed to detect it. Besides, publication bias generally is related to greater chance of a positive result, which did not occur in our systematic review.

Another shortcoming of the present study is the predefined exclusion of trials with biological agents. Recently, these drugs have increasingly gained part in the management of lung cancer. In the next few years, we expect results of new

sequential therapies with doublet chemotherapy such as with pemetrexed or docetaxel and the addition of other possible targeted therapies. The latest results are quite optimistic[27] and the desirable evolution to an individualised treatment seems to be achievable. All these new evidence may fairly change the prognosis of the patient with advanced disease and additional evaluation of this new therapeutic scenario will be warranted. Inherent limitations of post-progression treatment description precluded a valid analysis of the influence of second-line chemotherapy in the survival of patients.

In conclusion, the findings of this study corroborate the previous beliefs that the extension of first-line chemotherapy over three or 4 cycles does not improve overall survival. The use of shorter duration first-line therapy that offers equivalent survival will reduce the risk of toxicity what may negatively affect the quality of life. Four cycles of treatment with third-generation doublets can be considered the optimum duration of first-line treatment for advanced NSCLC.

Conflict of interest statement

None declared.

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