VOLUME 26 · NUMBER 28 · OCTOBER 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Chemotherapy in Addition to Supportive Care Improves Survival in Advanced Non–Small-Cell Lung Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 16 Randomized Controlled Trials

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Submitted April 24, 2008; accepted May 27, 2008; published online ahead of print at www.jco.org on August 4, 2008.

Supported by UK Medical Research Council.

Presented at 43rd Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 1-5, 2007, and at the World Conference on Lung Cancer, Seoul, South Korea, September 2-6, 2007.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/08/2628-4617/$20.00

DOI: 10.1200/JCO.2008.17.7162

ABSTRACT

Purpose
Since our individual patient data (IPD) meta-analysis (MA) of supportive care and chemotherapy for non–small-cell lung cancer (NSCLC), published in 1995, many trials have been completed. An updated, IPD MA has been carried out to assess newer regimens and determine conclusively the effect of chemotherapy.

Methods
Systematic searches for randomized controlled trials (RCTs) were undertaken, followed by central collection, checking, and reanalysis of updated IPD. Results from RCTs were combined to calculate individual and pooled hazard ratios (HRs).

Results
Data were obtained from 2,714 patients from 16 RCTs. There were 1,293 deaths among 1,399 patients assigned supportive care and chemotherapy and 1,240 among 1,315 assigned supportive care alone. Results showed a significant benefit of chemotherapy (HR, 0.77; 95% CI, 0.71 to 0.83; $P \leq .0001$), equivalent to a relative increase in survival of 23% or an absolute improvement in survival of 9% at 12 months, increasing survival from 20% to 29%. There was no clear evidence that this effect was influenced by the drugs used ($P = .63$) or whether they were used as single agents or in combination ($P = .40$). Despite changes in patient demographics, the effect of chemotherapy in recent trials did not differ from those included previously ($P = .77$). There was no clear evidence of a difference or trend in the relative effect of chemotherapy across patient subgroups.

Conclusion
This MA of chemotherapy in the supportive care setting demonstrates conclusively that chemotherapy improves overall survival in all patients with advanced NSCLC. Therefore, all patients who are fit enough and wish to receive chemotherapy should do so.

J Clin Oncol 26:4617-4625. © 2008 by American Society of Clinical Oncology

INTRODUCTION

Worldwide, approximately 1.5 million new cases of lung cancer are diagnosed each year.[1] Approximately 85% of these tumors are of non–small-cell histological type,[2] including adenocarcinomas, squamous cell, and large cell carcinomas. Non–small-cell lung cancer (NSCLC) is the main cause of death from cancer,[3] and 5-year survival across all stages of the disease is approximately 14%.[4]

Surgery is generally regarded as the best treatment option, but only approximately 30% of tumors are suitable for potentially curative resection.[5] A further 20% of patients, usually those presenting with locally advanced disease, undergo radical thoracic radiotherapy or combined chemoradiotherapy. The remaining 50% of patients, essentially those with metastatic disease or who are medically unfit, are treated palliatively.

Our previous meta-analysis[6] based on individual patient data (IPD) of more than 9,000 patients from more than 50 randomized trials, concluded that despite previous scepticism and controversy, platinum-based chemotherapy has a role in treating patients with NSCLC. In particular, there was strong evidence that for advanced disease, chemotherapy given in addition to supportive care could prolong survival. Since the publication, a considerable number of new trials exploring newer drugs and new modes of administration have been completed. To

take account of the expanded evidence base and provide the most up-to-date and reliable assessment of the role of chemotherapy in NSCLC, the NSCLC Collaborative Group has carried out an updated IPD meta-analysis that examines the role of chemotherapy in seven treatment comparisons.[7] In the supportive care setting reported here, we assessed the role of newer chemotherapy agents and assessed more reliably the effect of chemotherapy in different subgroups of patients.

METHODS

The aim was to assess the effect of supportive care and chemotherapy versus supportive care alone in advanced NSCLC. The meta-analysis followed a detailed and prespecified protocol which set out the objectives, inclusion criteria for trials, data to be collected and analyses to be carried out. A copy of the protocol is available on request (from S.B.).

Inclusion Criteria

To be included in the meta-analysis, trials had to be properly randomized, have commenced accrual on or after January 1, 1965, and have completed accrual. Trials should have included patients with NSCLC who had received either chemotherapy and supportive care or supportive care alone, that were unsuitable for surgery or radical radiation therapy. Supportive care was defined in the individual trials and may include palliative radiotherapy, antibiotics, corticosteroids, analgesics, antiemetics, transfusions, and psychosocial support. Patients should have not received any previous chemotherapy or had any prior malignancy.

Identification of Trials

To limit publication bias, we included all randomized trials, whether published or unpublished. We carried out bibliographic searches of Medline and CancerLit using the Cochrane Collaboration optimal search strategy for identifying randomized controlled trials.[8] These were supplemented by searching the Cochrane Central Register of Controlled Trials, the abstracts from relevant conferences, the reference lists of identified trials, the bibliographies of relevant books, and review articles. The National Cancer Institute Physicians Data Query clinical protocols, United Kingdom Coordinating Committee for Cancer Research trials register, and the Current Controlled Trials metaRegister of trials were also searched to identify unpublished and ongoing trials. All trialists who took part in the meta-analysis were asked to help to identify additional trials. Initially searches were completed for the period up to and including 2003. These were revised regularly to identify further trials published by our final analyses in September 2007. Where there was uncertainty about the eligibility of a trial or particular treatment arms within a trial, this was discussed and resolved by consensus within the Project Secretariat and International Advisory Group. We did not search for trials that used long-term alkylating agents. These were included in the 1995 analyses, but due to their antiquity, were not included in this update.

Data Collection

For trials already included in the 1995 analyses, updated follow-up was sought. Most of the trials previously provided mature data and we did not anticipate much additional information. However, some additional data were received and included in the new analyses.

For new trials, survival and baseline characteristics were sought for all patients randomly assigned into each trial. This included date of randomization, survival status, and date of last follow-up or death as well as information on date of birth, sex, performance status, tumor stage (TNM), and histological type.

Data Checking

A number of standard checks were applied to all new trials, including checks for missing values and data validity and consistency across variables. To assess the randomization integrity, we looked for unusual patterns in the sequencing of allocation or imbalances in baseline characteristics between treatment arms. Follow-up of surviving patients was also assessed to ensure that it was balanced by treatment arm and as up-to-date as possible. Any queries were resolved and the final database entries verified by the responsible trial investigator or statistician.

Definition of Outcomes

Overall survival was defined as the time from randomization until death by any cause. Patients still alive were censored at the date of last follow-up or date last known to be alive.

Analysis

Analyses of outcomes, trial groups, and patient groups were (unless otherwise stated) prespecified in the protocol and carried out on an intention to-treat basis; that is, patients were analyzed according to their allocated treatment, irrespective of whether they received that treatment. Analyses of all end points were stratified by trial, and the log-rank expected number of deaths and variance was used to calculate individual trial hazard ratios (HRs) and overall pooled HRs based on the fixed effect model.[9] Thus, the times to death for individual patients were used within trials to calculate the HR, representing the overall risk of an event for those patients allocated to supportive care and chemotherapy compared with those allocated to supportive care alone. Results were also combined using the random effects model to assess the robustness of the results to the choice of meta-analysis model.

To examine the potential impact of the treatments used, we predefined analyses that grouped trials by the type of the chemotherapy regimen used. For these analyses, a pooled HR was calculated for each group of trials and for all trials together. As we specified that we would group those trials using platinum-based chemotherapy with a vinca-alkaloid or etoposide separately from those trials that did not use a vinca-alkaloid or etoposide, the Big Lung Trial (BLT) trial[10] was divided into two trials. BLT1 combined cisplatin with a vinca-alkaloid and BLT2 did not use a vinca-alkaloid.

The relative effects of chemotherapy in different subgroups of patients were investigated using similar stratified analyses. Analyses were performed for each prespecified subgroup, for example, comparing the effect of treatment and control for males and for females within each individual trial. These results were then combined to give overall HRs for males and for females. χ^2 tests for interaction or trend were used to investigate whether there were any substantial differences in the effect of chemotherapy between groups of trials or subgroups of patients.

Results are also presented as absolute differences at 1 year, calculated using the overall HRs and the control arm event rate.[11] CIs for absolute differences were calculated from the baseline event rate and the HR at the 95% CI boundary values. χ^2 heterogeneity tests and the I^2 statistic for inconsistency[12] were used to assess statistical heterogeneity across trials. Survival curves are presented as simple (nonstratified) Kaplan-Meier curves.[13] All *P* values quoted are two sided.

Median follow-up was calculated by the reverse Kaplan-Meier method, based on surviving patients and using censoring as the event.

RESULTS

A total of 19 potentially eligible trials that had used supportive care and chemotherapy versus supportive care alone were identified. Data for two trials[14,15] were no longer available and for one trial,[16] adequate contact with the investigators could not be established.

Therefore, 16 trials that randomly assigned 2,714 patients were included (Table 1).[10,17-29] These represent 84% of patients from all known randomized trials that compared supportive care and chemotherapy with supportive care alone and 65% more data than that available in 1995. The 16 trials accrued between 32 to 447 patients. Characteristics of these trials are summarized in Table 1. Platinum-based chemotherapy was used in 12 trials (cisplatin in 11 and carboplatin in one[25]) and nonplatinum single agents (etoposide, vinorelbine, gemcitabine, and paclitaxel) were used in four trials.

Patients' characteristics for the 2,714 patients across all trials are presented in Table 2. Data for age and sex were provided for all trials.

Table 1. Characteristics of Included Trials

Trial	Inclusion Period	No. of Patients Accrued	Chemotherapy Used	Chemotherapy Dose Per Cycle (mg/m^2)	Maximum No. of Cycles	Stage (%)				Performance Status (%)		Histology (%)			Age (%)	
						I, II	IIIa	IIIb	IV	0,1	≥ 2	Squamous	Adeno	Other	< 70	≥ 70
Using platinum + vinca-alkaloid/ etoposide																
RLW 8351[17]	1982-1986	167	Cisplatin	120	P/T	0	0	100	0	73	27	37	37	26	88	12
			Vindesine	3												
NCIC CTG BR5[18]	1983-1986	150	Cisplatin	120	P/T	0	0	13	85	60	40	29	43	27	98	2
			Vindesine	3												
			or													
			Cisplatin	40												
			Doxorubicin	40												
			Cyclophosphamide	400												
Southampton[17]	1983-1986	32	Cisplatin	120	6	0	0	100	0	81	1	50	34	15	91	9
			Vinblastine	3	15											
NRH[19]	1983-1987	87	Cisplatin	70	4	0	2	0	48	60	40	40	39	21	89	11
			Etoposide	100												
Ancona 1[20]	1985-1988	128	Cisplatin	80	P/T	0	0	41	59	88	12	NK	NK	NK	95	5
			Cyclophosphamide	500												
			Epirubicin	50												
			alternating with													
			Methotrexate	30												
			Etoposide	200												
			Lomustine	70 (orally)												
CEP-85[22]	1985-1988	49	Cisplatin	120	8	0	2	0	94	67	27	47	33	14	84	16
			Vindesine	3	18											
UCLA[23]	1984-1986	63	Cisplatin	120	P/T	0	0	0	100	67	10	40	54	6	63	11
			Vinblastine	6												
JLCSG[25]	1990-1995	48	Carboplatin	300	8	0*	0*	9*	91*	NK	NK	NK	NK	NK	76	23
			Etoposide	120 × 2												
BLT1[10]	1995-2001	477	Cisplatin	80	3	3	20	36	38	82	25	56	24	25	76	31
			Vindesine	3 × 2												
			or													
			Cisplatin	80	3											
			Vinorelbine	30 × 2												
			or													
			Cisplatin	50	3											
			Mitomycin C	6												
			Vinblastine	6												
Using other platinum regimen																
AOI-Udine[21]	1984-1986	102	Cisplatin	75	6	0	0	0	100	49	51	48	35	17	98	2
			Mitomycin C	10												
			Cyclophophamide	400												
MIC2[24]	1988-1996	359	Cisplatin	50	4	NK	NK	NK	NK	64	28	56	27	19	84	19
			Mitomycin C	6												
			Ifosfamide	3 (g/m^2)												
BLT2[10]	1995-2001	248	Cisplatin	50	3	2	30	30	36	71	19	46	22	19	56	33
			Mitomycin C	6												
			Ifosfamide	3 (g/m^2)												
Using vinca-alkaloid/ etoposide only																
Gwent 2[26]	1982-1984	186	Etoposide	600	6	24	12	10	33	87	8	100	0	0	84	13
ELVIS[27]	1996-1997	161	Vinorelbine	30 × 2	6	0	1	15	60	63	21	36	29	26	< 1	84
Using anti-metabolic agent only																
Manchester 1[28]	1994-1996	300	Gemcitabine	1,000 × 3	6	NK	NK	NK	40*	94	6	NK	NK	NK	69	31
Using taxane only																
Manchester 2[29]	1995-1997	157	Paclitaxel	200	P/T	0	0	45	55	81	19	47	29	20	66	34

NOTE. Totals may not add up to 100% due to missing/unknown data.

Abbreviations: Adeno, adenocarcinoma; NK, not known; P/T, until progression or toxicity; NCIC CTG, National Cancer Institute of Canada Clinical Trials Group; NRH, Norwegian Radium Hospital; CEP-85, Cerce d'etudes pneumologiques; UCLA, University of California—Los Angeles; JLCSG, Joint Lung Cancer Study Group; BLT, Big Lung Trial; AOI, Associazione Oncologia Italiana; MIC2, mitomycin, ifosfamide, and cisplatin; ELVIS, Elderly Lung Cancer Vinorebine Italian Study Group.

*Information from publication not from data supplied.

Table 2. Characteristics of Included Patients

Characteristic	Supportive Care Plus Chemotherapy		Supportive Care Alone	
	No.	%	No.	%
Age, years				
< 60	509	36	448	34
60-64	259	19	236	18
65-69	274	20	272	21
> 70	346	24	349	26
Unknown	11	< 1	10	< 1
Sex				
Male	1,076	77	984	75
Female	313	22	322	24
Unknown	10	< 1	9	< 1
Histology				
Adenocarcinoma	320	23	300	23
Squamous	605	43	554	42
Mixed	1	< 1	2	< 1
Large cell undifferentiated	96	7	73	5
NSC unspecified	22	1	36	3
Other	105	7	93	7
Unknown	39	3	40	3
Data not supplied	211	15	217	16
Stage				
I	18	1	14	1
II	22	2	14	1
IIIa	92	7	106	8
IIIb	337	24	300	23
IV	508	36	466	35
Unknown	73	5	58	5
Data not supplied	349	25	357	27
Performance status				
0	347	25	299	23
1	687	49	670	51
2	290	21	263	20
3	19	1	20	1
4	1	< 1	1	< 1
Unknown	33	2	36	2
Data not supplied	22	1	26	2

Abbreviation: NSC, non–small-cell.

Histology data were provided for 15 trials and performance status and stage were supplied for 13 trials. Based on these available data, patients were mostly male, age between 60 and 70 years, with good performance status. Performance status was defined as good (WHO/Eastern Cooperative Oncology Group 0 or 1, Karnofsky 100 to 70) or poor (WHO/Eastern Cooperative Oncology Group 2+, Karnofsky 60 or lower).

Of the stage data we received, 90% of patients had tumors that were advanced (predominantly stage IIIb and IV). However, there was a small proportion (3%) of patients had stage I and II disease. This appears to be because some trials[10,26] did not restrict entry to advanced patients and these individuals were (presumably) randomly assigned because their condition precluded or the patient declined surgery or radical radiation therapy.

Most patients had squamous cell tumors (43%) or adenocarcinomas (23%), the proportion of these tumor types has not substantially changed between 1995 and the current analysis.

The median follow-up for all surviving patients was 1 year 4 months (range, < 1 month to 9.5 years).

Overall Survival

Survival analyses were based on 2,533 deaths and 2,714 patients from 16 trials. Figure 1 shows a highly statistically significant benefit of chemotherapy on survival (HR, 0.77; 95% CI, 0.71 to 0.83; $P < .0001$) translating to an absolute improvement of 9% at 12 months increasing survival from 20% to 29% or an absolute increase in median survival of 1.5 months (from 4.5 months to 6 months). There was some evidence of heterogeneity between the trials ($P = .02$; $I^2 = 47\%$). However, repeating the sensitivity analysis carried out in 1995,[6] which excluded the extreme results of CEP-85[22] (49 patients) resulted in considerably lower heterogeneity ($P = .275$; $I^2 = 16\%$) with a similar effect of chemotherapy on overall survival (HR, 0.78; 95% CI, 0.72 to 0.85). Also, based on all trials, results using the random effects model were similar (HR, 0.75; 95% CI, 0.67 to 0.84; $P < .0001$). The survival curve is shown in Figure 2.

There was no clear evidence of a difference in the effect of chemotherapy between chemotherapy types (Fig 1; $P = .63$) or between trials that used combination chemotherapy and those that used single agent chemotherapy (Table 3; $P = .40$).

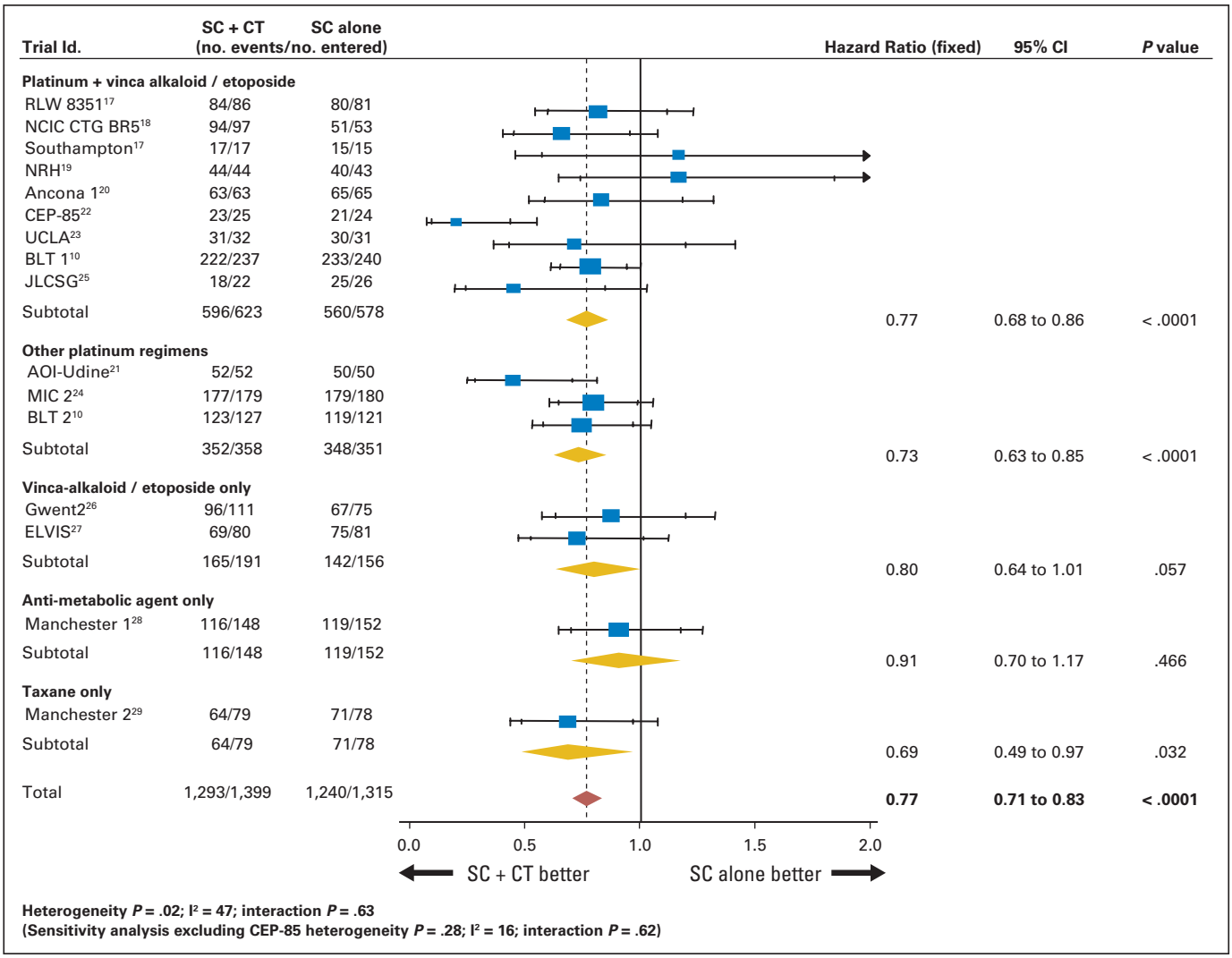

Fig 1. Hazard ratio plot of effect of chemotherapy on survival. Each trial is represented by a blue square, the center of which denotes the hazard ratio for that trial with the horizontal lines showing the 99% and 95% CIs. The size of the square is directly proportional to amount of information in the trial. The red diamond gives the overall hazard ratio for combined results of all trials; the center denotes the hazard ratio and the extremities the 95% CI. The yellow diamonds represent hazard ratios for the trial groups; the center denotes the hazard ratio and the extremities the 95% CI. SC, supportive care; CT, chemotherapy; NCIC CTG, National Cancer Institute of Canada Clinical Trials Group; NRH, Norwegian Radium Hospital; CEP-85, Cerce d'etudes pneumologiques; UCLA, University of California—Los Angeles; JLCSG, Joint Lung Cancer Study Group; BLT, Big Lung Trial; AOI, Associazione Oncologia Italiana; MIC2, mitomycin, ifosfamide, and cisplatin; ELVIS, Elderly Lung Cancer Vinorebine Italian Study Group.

Of the three trials that we could not include in these analyses, we could estimate a HR for survival[30] for one trial[16] of 207 patients. This trial used single-agent docetaxel, had a reported $P = .03$ and gave a very similar result (HR, 0.70; 95% CI, 0.51 to 0.95) to the included trial[29] that used a single-agent taxane (HR, 0.69; 95% CI, 0.49 to 0.97).

Since the 1995 meta-analysis, the patient demographic may have changed, and so the effect of chemotherapy may also have changed. Certainly, there was a higher proportion of patients older than 70 in the more recent trials, probably due to aging populations and widening eligibility criteria, although all trials included patients older than 70 years (Table 1). The median age of patients in the trials included since the 1995 analysis was higher (66 years old, previously 61 years old), there were more women (28%, previously 19%), and far more stage IIIa patients (16%, previously 3%). There was no real change in the proportion of patients with adenocarcinoma or squamous cell histology. Despite these differences, there was no evidence of a difference in effect of chemotherapy between trials in the 1995 analysis and the recent trials (interaction $P = .77$) or between previous platinum-based trials and recent platinum-based trials (interaction $P = .64$) (Table 3).

Patient Subgroups

There was no clear evidence of a difference or trend in the relative effect of chemotherapy in patient subgroups defined by age ($P = .64$), sex ($P = .77$), stage ($P = .35$), histology ($P = .75$), or performance status ($P = .54$; Fig 3). Furthermore, despite the difference in underlying survival by performance status, the absolute effect at 12 months was fairly similar; 8% for performance status 0/Karnofsky 100 to 90 (from 26% to 34%), 8% for 1/Karnofsky 80 to 70 (from 18% to 26%), and 6% for 2+/Karnofsky 60 or lower (from 8% to 14%).

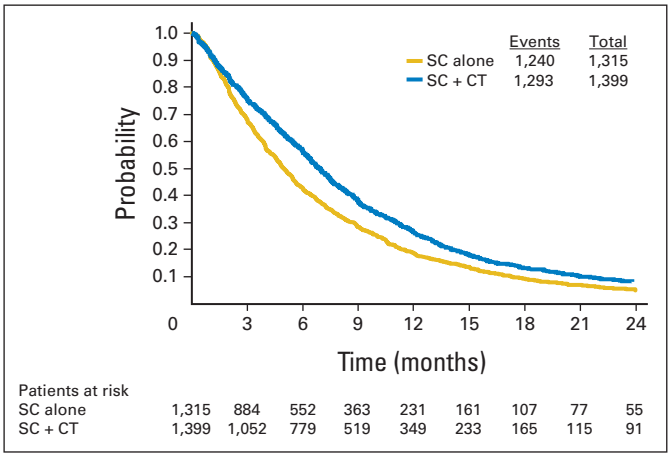

Fig 2. Simple (nonstratified) Kaplan-Meier curve for survival by treatment. SC, supportive care; CT, chemotherapy.

DISCUSSION

Based on 16 trials and 2,714 patients, this systematic review and meta-analysis includes 65% more data than that available in 1995 and represents the most comprehensive and reliable review of chemotherapy in the supportive care setting. Results demonstrate a substantial benefit of chemotherapy for advanced NSCLC, improving survival by 9% at 12 months and median survival by 1.5 months. The benefit seen in new trials is consistent with that seen previously, despite changes in the lung cancer population and drug regimens used over time.

We now have substantially more power to look at the effect of chemotherapy in different groups of patients and can be more confident on these results than in 1995. Both the relative and absolute benefits of chemotherapy are remarkably consistent across patient subgroups, notably with benefits irrespective of age and performance status.

In our meta-analysis, the effectiveness of newer drugs such as vinorelbine, paclitaxel, and gemcitabine, used as single agents appears to be similar to that of platinum-based chemotherapy combined with older agents, such as vindesine and mitomycin C, potentially offering a greater range of treatment options and candidates for future trials. However, individually only one trial using single-agent paclitaxel[29] is statistically significant in favor of chemotherapy ($P = .03$) and another using vinorelbine[27] is of borderline significance ($P = .06$). The trial of single-agent docetaxel,[16] that we could not include was also significantly in favor of chemotherapy ($P = .03$).

In 1998, a meta-analysis that compared single agent and combination chemotherapy in advanced NSCLC[31] found that while the response rate for patients receiving combination chemotherapy was improved, overall survival was not significantly better. There was also increased toxicity associated with combination chemotherapy. Similarly, this meta-analysis suggests no difference in effect between trials using single-agent and combination chemotherapy, however, our observation is an indirect comparison. Two more recent literature-based meta-analyses[32,33] both reported that two agents were more beneficial than one, but that three agents were no more beneficial than two.[33] It is important to remember however, that these observations are based on indirect comparisons and the power to detect any differences is limited. Thus, this conclusion should be interpreted with caution.

A number of trials have been completed or are still ongoing which compare newer agents, such as docetaxel and gemcitabine, in combination or as single agents. One completed trial[34] of carboplatin and paclitaxel versus paclitaxel alone suggested that although there was no evidence of a difference in effect between the treatments, combination chemotherapy could be an option for those able to tolerate a more aggressive treatment.

In the 1995 analysis, the platinum-based trials showed a 27% reduction in the risk of death equivalent to an increase in median survival of 1.5 months. This led to discussion about the impact on quality of life and whether the adverse effects of chemotherapy were worthwhile for this relatively small increase in survival. At that time, only two[22,23] of the included trials had tried to measure quality of life and both had failed to do so successfully. Although we did not collect quality of life data, three trials using platinum-based chemotherapy[10,24,25]one using vinorelbine,[27] one using gemcitabine,[28] and one using paclitaxel,[29] which have been included since 1995, assessed quality of life. Of the trials we could not include, one trial of docetaxel[16] and one of platinum-based chemotherapy[14] also assessed quality of life. All reported that quality of life was either no worse or improved for those patients receiving chemotherapy. This suggests that platinum-based regimens and newer agents could offer both improved survival and possibly better quality of life.

Table 3. Exploratory Analysis of the Effect of Chemotherapy on Survival

Trial Group	No. of Trials	No. of Patients	Hazard Ratio	95% CI	*P*	*P* for Interaction
Period of trials (all trials)						**.77**
All trials included in 1995	9	964	0.76	0.66 to 0.87	.0006	
All trials included since 1995	6	1,750	0.77	0.70 to 0.86	< .0001	
Period of trials (platinum-based trials)						**.64**
Platinum-based trials included in 1995	8	778	0.73	0.63 to 0.85	< .0001	
Platinum-based trials included since 1995	3	1,132	0.77	0.68 to 0.86	< .0001	
Chemotherapy type (all trials)						**.40**
Combination chemotherapy	11	1,910	0.75	0.68 to 0.83	< .0001	
Single-agent chemotherapy	4	804	0.81	0.70 to 0.95	.008	

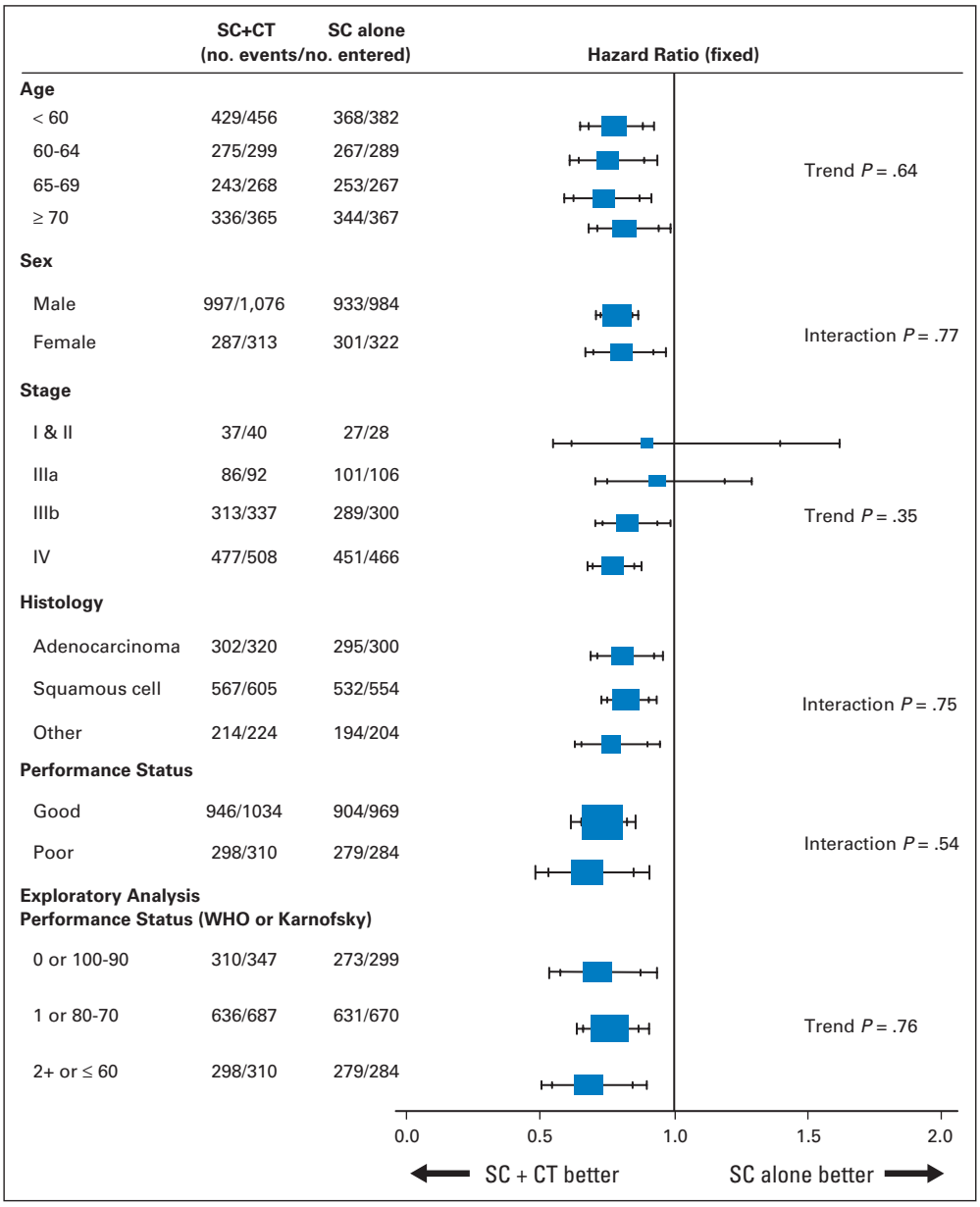

Fig 3. Effect of chemotherapy on survival by age, sex, stage, histology, and performance status.

The current meta-analysis suggests that we do not need another trial of supportive care alone versus supportive care and chemotherapy. What we do need are more trials comparing third generation chemotherapy combinations, doses, and duration, and also further research on toxicity and adverse effects. Recent trials have shown the efficacy of epidermal growth factor receptor tyrosine kinase inhibitors in patients with advanced cancer[35] who have relapsed after first-line chemotherapy and so future trials may also exploit these encouraging developments.

This meta-analysis demonstrates conclusively that chemotherapy increases overall survival for all types of patients with advanced NSCLC and that there should be no change in the treatment paradigm. Evidence from trials that collected quality of life data also suggests that this approach is unlikely to be detrimental to the patients' quality of life. Therefore, all patients who are fit enough and wish to receive chemotherapy, should do so.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Thierry Le Chevalier, GlaxoSmithKline (U) **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** Richard Stephens, Pierre Fabre Oncology **Research Funding:** Max Parmar, UK Medical Research Council; Jean-Pierre Pignon, Sanofi-aventis; Richard Stephens, UK Medical Research Council **Expert Testimony:** None **Other Remuneration:** None

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Acknowledgment

The NSCLC Meta-Analyses Collaborative Group (composition below) thanks all patients who took part in the trials and contributed to this research. The meta-analysis would not have been possible without their participation or without the collaborating institutions that provided their trial data.

The meta-analysis was funded by the United Kingdom Medical Research Council.

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