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Chemotherapy versus supportive care in advanced non-small cell lung cancer: improved survival without detriment to quality of life

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Background: In 1995 a meta-analysis of randomised trials investigating the value of adding chemotherapy to primary treatment for non-small cell lung cancer (NSCLC) suggested a small survival benefit for cisplatin-based chemotherapy in each of the primary treatment settings. However, the meta-analysis included many small trials and trials with differing eligibility criteria and chemotherapy regimens.

Methods: The aim of the Big Lung Trial was to confirm the survival benefits seen in the meta-analysis and to assess quality of life and cost in the supportive care setting. A total of 725 patients were randomised to receive supportive care alone (n=361) or supportive care plus cisplatin-based chemotherapy (n=364).

Results: 65% of patients allocated chemotherapy (C) received all three cycles of treatment and a further 27% received one or two cycles. 74% of patients allocated no chemotherapy (NoC) received thoracic radiotherapy compared with 47% of the C group. Patients allocated C had a significantly better survival than those allocated NoC: HR 0.77 (95% CI 0.66 to 0.89, p=0.0006), median survival 8.0 months for the C group v 5.7 months for the NoC group, a difference of 9 weeks. There were 19 (5%) treatment related deaths in the C group. There was no evidence that any subgroup benefited more or less from chemotherapy. No significant differences were observed between the two groups in terms of the pre-defined primary and secondary quality of life end points, although large negative effects of chemotherapy were ruled out. The regimens used proved to be cost effective, the extra cost of chemotherapy being offset by longer survival.

Conclusions: The survival benefit seen in this trial was entirely consistent with the NSCLC meta-analysis and subsequent similarly designed large trials. The information on quality of life and cost should enable patients and their clinicians to make more informed treatment choices.

In 1995 the Non-Small Cell Lung Cancer Collaborative Group combined the results of 52 randomised trials that compared first line treatment for non-small cell lung cancer (NSCLC) with or without the addition of chemotherapy. The results of this meta-analysis showed a survival benefit with cisplatin-based chemotherapy in all four settings (patients receiving surgery, surgery and radiotherapy, radical radiotherapy, and supportive care).¹ Although the survival benefit was statistically significant in the radical radiotherapy and supportive care settings, the increase in median survival was small. Furthermore, the meta-analysis included mainly small trials and trials with differing eligibility criteria and chemotherapy regimens. The rationale for setting up the Big Lung Trial was to confirm the survival benefits suggested by the meta-analysis by running one large trial in all the above settings, making it open to all patients with NSCLC.

The trials of supportive care with or without chemotherapy included in the meta-analysis provided scant information on quality of life and cost. This highlighted the lack of certainty about whether the modest survival advantage from chemotherapy in advanced NSCLC had a positive or negative impact on quality of life, and hence provided no clear lead for the management of this large group of patients. In the supportive care setting of the Big Lung Trial the design therefore included large sub-studies assessing quality of life and cost.

METHODS

Eligibility

The trial was designed to be as inclusive as possible. Thus, the only eligibility criteria for entry into the supportive care

setting were that the patient: (1) fulfilled the local criteria for histological or cytological diagnosis of NSCLC; (2) was considered unsuitable for, or declined, radical radiotherapy or surgery; (3) was considered fit to receive chemotherapy; and (4) had no concurrent malignancy or history of malignancy other than non-melanomatous skin cancer within the last 3 years. In addition, both the doctor and patient had to be uncertain about the value of chemotherapy.

Patients included in this setting were all those for whom supportive care was the treatment of choice so accrual was not confined to a particular clinical stage or performance status. Patients with stage I or II NSCLC could therefore be included if the patient had declined more radical treatment or if co-morbidity excluded it. The trial therefore reflected the diversity of practice in the UK over its duration.

Multicentre and local research ethics committee approval was obtained, together with individual written informed patient consent.

Trial design

This was a large multicentre randomised trial comparing supportive care alone with supportive care plus cisplatin-based chemotherapy. The choice of chemotherapy regimen (from one of four cisplatin-based regimens) could be made on a patient by patient basis but had to be stated before randomisation. Randomisation was performed by telephoning either the London Lung Cancer Group Trials Office or the Cancer Division of the Medical Research Council Clinical Trials Unit. Patients were stratified by centre, choice of chemotherapy regimen, sex, histology, performance status,

and whether the patient was taking part in the quality of life sub-study. The allocation was to: (1) supportive care alone (NoC) or (2) supportive care plus three cycles of 3 weekly chemotherapy (C).

Supportive care alone

Patients could receive any treatment including palliative radiotherapy—but not chemotherapy—that was considered appropriate by their clinician.

Supportive care plus chemotherapy

In addition to supportive care, patients were prescribed three cycles of 3 weekly cisplatin-based chemotherapy. At the start of the trial (in November 1995) three chemotherapy regimens, all widely used in the UK, were permitted. However, as new drugs became available, a further regimen—vinorelbine (Navelbine) plus cisplatin—was added in October 1997.

The regimens were:

- MIC: day 1: cisplatin 50 mg/m², mitomycin 6 mg/m², ifosfamide 3 g/m²;
- MVP: day 1: cisplatin 50 mg/m², mitomycin 6 mg/m², vinblastine 6 mg/m²;
- CV: day 1: cisplatin 80 mg/m², vindesine 3 mg/m²; day 8: vindesine 3 mg/m²;
- NP: day 1: cisplatin 80 mg/m², vinorelbine 30 mg/m²; day 8: vinorelbine 30 mg/m².

Reports and investigations

This was a large trial and only essential data were collected. At randomisation all the baseline clinical data (age, sex, TNM stage, histology, WHO performance status (PS), and choice of chemotherapy regimen) were collected over the telephone. Patients were staged according to local practice. Data on primary and protocol treatment were collected for all patients 3 months after randomisation and included details of chemotherapy (if received), immediate palliative radiotherapy, and any grade 3/4 toxicities experienced. Subsequent follow up forms requesting details of date and site of progression and survival were completed 6 months after randomisation, at 1 year, and then annually.

Statistical analysis

The primary end point was overall survival. Quality of life and costs were investigated within optional sub-studies.

All analyses were performed on an intention-to-treat basis. Survival was measured from date of randomisation to date of death (from all causes), or the date last seen for surviving patients. The Kaplan-Meier method was used to calculate the survival curves and the Mantel-Cox version of the log rank test to make treatment comparisons. Subgroups of patients were compared in terms of their hazard ratios (HRs) and 95% and 99% confidence intervals (CIs) for survival.

A total of 800 patients was required to reliably detect an improvement in median survival from 4 months with supportive care alone to 5 months with supportive care plus chemotherapy (two sided test, 5% significance level, 80% power).

An independent data monitoring and ethics committee consisting of two clinicians not entering patients into the trial, an independent statistician, and a quality of life expert was set up. They met at approximately yearly intervals to review the interim data, advise on the safety of the regimens, consider whether adjustments to the protocol were required, and recommend the continuation or closure of the trial.

Sub-studies

Quality of life sub-study

Patients participating in the optional quality of life sub-study completed the EORTC QLQ-C30 and LC17 questionnaires^{2,3} at

baseline (after consent but before randomisation) and at 6–8, 12, 18, and 24 weeks after randomisation. They also completed daily diary cards for the first 12 weeks after randomisation. The daily diary cards were based on the MRC cards⁴ and related to nine key lung cancer symptoms and concerns (nausea, vomiting, tiredness, breathlessness, mood, overall condition, appetite, activity, and difficulty swallowing).

Because of funding difficulties the quality of life study did not begin until March 1998. After that time, details of patients who agreed to participate in the quality of life sub-study were faxed from the randomising centre to the Clinical Trials and Research Unit at the University of Leeds who conducted this part of the Big Lung Trial.

A priori quality of life hypotheses were generated by surveying selected participating clinicians. Based on this survey, the primary end point was defined as global quality of life at 12 weeks, and highlighted end points were emotional and physical functioning and symptoms of fatigue, dyspnoea, and pain at 12 weeks. Primary and highlighted end points were compared using multi-level repeated measures modelling (allowing for time, treatment, treatment by time interaction, adjusting for baseline quality of life (all fixed effects), patient and patient by time (random effects)). Clinicians indicated that only large differences in the quality of life end points would be of clinical interest. Using the definitions based on King⁵ and Osoba *et al.*,⁶ a large difference between the two groups translated into an effect size (difference in means divided by the standard deviation of either group) of 0.4–0.5 and, allowing for a compliance rate of 65% at 12 weeks, this required approximately 300 patients (two sided test, 5% significance, 80% power).

Cost sub-study

To investigate the cost implications of adding chemotherapy to supportive care, a study of costs was carried out by the York Health Economics Consortium in selected high recruiting centres. Data on individual patient resource use were collected retrospectively from randomisation until death (or to 2 years if the patient was still alive at this time point). Data collected included the number and duration of inpatient admissions, use of chemotherapy, radiotherapy details, investigations, outpatient visits, day cases (e.g. for pleural aspiration or blood transfusion), surgical procedures, and hospice inpatient care. A total of 200 patients was estimated to be sufficient to detect an economically meaningful difference in mean costs between the two groups (two sided test, 5% significance level, 80% power).

RESULTS

Accrual

Between November 1995 and November 2001 a total of 725 patients entered into the supportive care setting of the Big Lung Trial from 57 UK and five non-UK centres. The decision to close the trial on the planned closure date, but before the target of 800 supportive care patients had been reached, was taken as funding ceased in November 2001 and accrual to the whole Big Lung Trial had slowed. The Independent Data Monitoring and Ethics Committee considered that the additional information obtained by keeping the trial open would be offset by the opportunity to report the results earlier. 361 patients were randomised to receive no chemotherapy (NoC) and 364 to chemotherapy (C).

Patient characteristics

The main baseline patient characteristics are listed in table 1. The median age was 65 years and the majority of patients were male (74%) with stage III or IV disease (95%), squamous histology (53%), and WHO PS 0 or 1 (78%). All

Table 1 Baseline patient characteristics

	C	NoC
Age (years)		
Median	65.2	65.8
<55	47 (13%)	49 (14%)
55–64	132 (36%)	117 (32%)
65–74	153 (42%)	167 (46%)
≥75	32 (9%)	28 (8%)
Sex		
Male	275 (76%)	260 (72%)
Female	89 (24%)	101 (28%)
Clinical stage		
I	6 (2%)	6 (2%)
II	14 (4%)	12 (3%)
IIla	67 (19%)	87 (24%)
IIlb	135 (38%)	111 (31%)
IV	136 (38%)	136 (39%)
Uncertain	6	9
Histology		
Squamous	194 (54%)	185 (52%)
Adenocarcinoma	80 (22%)	89 (25%)
Other	84 (23%)	83 (23%)
Unknown	6	4
WHO PS		
0	79 (22%)	88 (24%)
1	205 (56%)	191 (53%)
2	72 (20%)	75 (21%)
3	8 (2%)	7 (2%)

C, chemotherapy; NoC, no chemotherapy; PS, performance status.

the characteristics were well balanced between the two groups.

The proportion of patients with WHO PS ≥2 and the proportion of patients aged 70 years or more being entered remained constant throughout the duration of the trial.

Choice of chemotherapy regimen

At the time each patient was randomised the clinician was asked to state which chemotherapy regimen would be used if chemotherapy was subsequently allocated. The choices are shown in table 2.

Only a few centres used the CV regimen in the first 2 years of the trial. Over the course of the trial, NP (which was only introduced 2 years into the trial) and MVP were increasingly used at the expense of MIC, which was used in fewer than 10% of patients in the final year of the trial.

Chemotherapy

Of the 364 patients allocated to receive chemotherapy, 238 (65%) received their prescribed three cycles of the regimen chosen before randomisation. A further 42 patients (12%) received two cycles, 54 (15%) received one cycle, 24 (7%) received no chemotherapy, and the remaining six patients (2%) received a different regimen from that chosen.

Of the 238 patients who received all three cycles of chemotherapy, 177 (74%) did so without any modifications (a reduction in the dose of any drug of >10%) or delays (of more than 7 days), 22 (9%) patients with modification, 25 (11%) with delay, and 14 (6%) with both.

The reasons for stopping after one or two cycles were: died mid chemotherapy cycle (n = 31), toxicity (n = 20), patients' request (n = 16), progressive disease (n = 15), clinical decision (n = 7), and for the remaining seven patients no details are available. The reasons for receiving no chemotherapy were: deterioration or death in the period between randomisation and starting chemotherapy (n = 13), patient refused chemotherapy (n = 6), and patient considered to have become unsuitable for chemotherapy (n = 5).

The median time from randomisation to starting chemotherapy was 7 days with 87% of patients starting chemotherapy within 14 days.

Table 2 Choice of chemotherapy regimen

	C	NoC
CV	16 (4%)	18 (5%)
MIC	127 (35%)	121 (34%)
MVP	153 (42%)	151 (42%)
NP	68 (19%)	71 (20%)

C, chemotherapy; NoC, no chemotherapy. For details of chemotherapy regimens, see text.

Table 3 shows that patients with an initial WHO PS of 0 or 1 received more cycles of chemotherapy than those with PS 2 or 3 (74% of PS 0/1 patients received three cycles compared with only 41% of PS 2/3 patients). Very similar proportions (69%) of patients receiving CV, MIC or MVP received all three cycles compared with only 55% of those on NP.

Eight of the 361 patients allocated to NoC actually received chemotherapy. This was a clinical decision (n = 4) or at the patient's request (n = 4).

Radiotherapy

Significantly more NoC patients received thoracic radiotherapy (n = 268 (74%)) than C patients (n = 171 (47%)). The doses of thoracic radiotherapy received were similar in the two groups. In the C group 29% of patients received <20 Gy, 30% received 20–29 Gy, and 41% received ≥30 Gy compared with 34%, 23%, and 43%, respectively, in the NoC group. Similar numbers of patients in both groups (16 C (4%) and 15 NoC (4%)) received non-thoracic radiotherapy.

Toxicity

Toxicity was much as expected for cisplatin-based regimens. 31% of patients were reported as experiencing grade 3/4 toxicity, mainly haematological (14%), nausea/vomiting (4%), neurological (2%), and renal toxicity (1%). Patients receiving two-drug regimens experienced more grade 3/4 toxicity than those on three-drug regimens (44% v 28%).

Survival

At the time of analysis 697 (96%) patients had died. The median follow up time for the 28 survivors is 23 months. The overall survival plot is shown in fig 1. The overall HR was 0.77 (95% CI 0.66 to 0.89), p = 0.0006. The median survival was 8.0 months for C patients and 5.7 months for NoC patients; 1 and 2 year survival figures were 29% and 10%, and 20% and 5% for the C and NoC groups, respectively.

Survival was also related to stage (p = 0.0002) and WHO PS (p = 0.0001), and patients with squamous histology survived longer than those with adenocarcinoma (p = 0.008). However, there was no evidence that survival was related to age (p = 0.49), sex (p = 0.33), or chosen chemotherapy regimen (p = 0.99).

Causes of death

In the C group 298 (86%) of the patients who died were reported as dying of lung cancer, but there were 14 (4%) treatment related deaths and 33 (10%) patients were reported as dying of other causes. In the NoC group 338 (96%) were reported as dying of lung cancer, one (0.3%) of a treatment related cause, and 13 (4%) of other causes.

In view of the large number of deaths from other causes, the information on events leading up to death was reviewed by three of the participating clinicians and the re-categorisation of death is shown in table 4.

Fourteen patients in the C group were reported as having a treatment related death and a further five patients who were recorded as dying of other causes were re-classified as treatment related deaths, making a total of 19 (5%) patients.

Table 3 Cycles of chemotherapy received according to baseline WHO performance status (PS) and chosen chemotherapy regimen (based on 358 patients who were allocated and received their chosen chemotherapy regimen)

Cycles received	Performance status			
	PS 0 (n = 79)	PS 1 (n = 200)	PS 2 (n = 71)	PS 3 (n = 8)
0	3 (4%)	9 (5%)	10 (14%)	2 (25%)
1	7 (9%)	26 (13%)	19 (27%)	2 (25%)
2	11 (14%)	17 (9%)	14 (20%)	0 (0%)
3	58 (73%)	148 (74%)	28 (39%)	4 (50%)

Cycles received	Chosen regimen			
	CV (n = 16)	MIC (n = 123)	MVP (n = 153)	NP (n = 66)
0	1 (6%)	7 (6%)	11 (7%)	5 (8%)
1	2 (12%)	15 (12%)	22 (14%)	15 (23%)
2	2 (12%)	16 (13%)	14 (9%)	10 (15%)
3	11 (69%)	85 (69%)	106 (69%)	36 (55%)

For details of chemotherapy regimens, see text.

Despite the small numbers, it is important to try and identify potential subgroups of patients who are at a high risk of a treatment related death. Exploratory analyses suggested that patients with a poor baseline WHO performance status and those receiving two-drug regimens were more at risk of a treatment related death than those with a WHO performance status of 0 or 1 or those receiving three-drug regimens (PS 0/1 patients 2.8%, PS 2/3 7.5%, two-drug regimens 6.1%, three-drug regimens 3.2%).

Interactions

Hypothesis generating survival analyses of subgroups of patients, as defined by the baseline characteristics listed in table 1, were undertaken. Figure 2 shows the HRs and 95% and 99% CIs for age, sex, stage of disease, WHO performance status, histology, and chosen chemotherapy regimen. There was no evidence that any subgroup benefited significantly more or less from chemotherapy.

Quality of life sub-study

Patient sample

Two hundred and seventy three patients (135 C, 138 NoC) from 32 UK and one Australian centre were entered into the

quality of life study. There were no differences in baseline clinical characteristics between the two treatment arms or between patients in and not in the quality of life sub-study. However, at baseline, patients allocated to the C group reported better quality of life and fewer symptoms than the NoC patients. As the baseline quality of life was collected before randomisation, these differences must be due to chance and adjustments in the analyses were performed to take account of these differences.

Primary end point

For the primary end point baseline and 12 week data were available for 134 patients (68 C, 66 NoC). The mean standardised global quality of life score (range 0–100) at 12 weeks was 52.1 for C patients and 48.2 for NoC patients (higher score representing a better quality of life), a difference of 3.9 (95% CI –3.9 to 11.7), $p = 0.4$ in favour of chemotherapy (table 5, fig 3). According to King,⁵ a difference of 10 points in score represents a large difference in global quality of life. Some sensitivity analyses around the missing data indicate a potential for a large detrimental effect, but all analyses indicate the potential for a large positive effect at 12 weeks.

Highlighted end points

Table 5 and fig 3 also show the mean standardised scores at baseline and at 12 weeks for the five highlighted end points. No statistically significant differences were observed. Large differences have been defined as ± 25 points for physical functioning, ± 7 points for emotional functioning, and ± 20 points for dyspnoea, fatigue and pain.⁵ The 95% CIs indicate

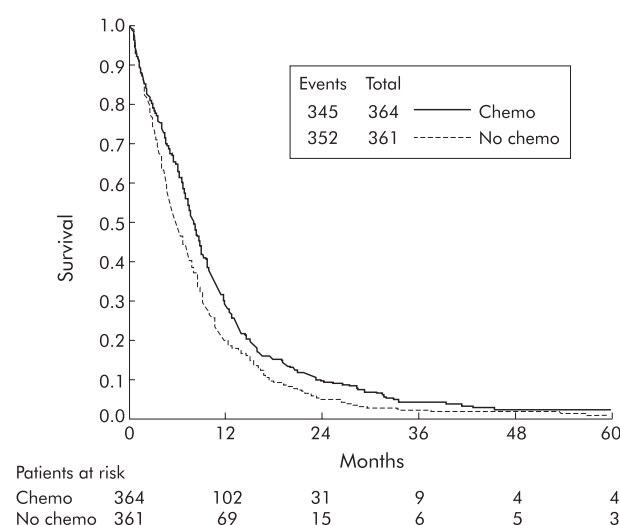


Figure 1 Overall survival.

Table 4 Re-categorisation of deaths originally recorded as due to "other causes"

	C (n = 33)	NoC (n = 13)
Lung cancer	11	6
First line chemotherapy	5	0
Other treatment	2	1
Vascular event	8	2
GI related	2	2
Other cancer	4	2
Respiratory infection	1	0
Total	33	13

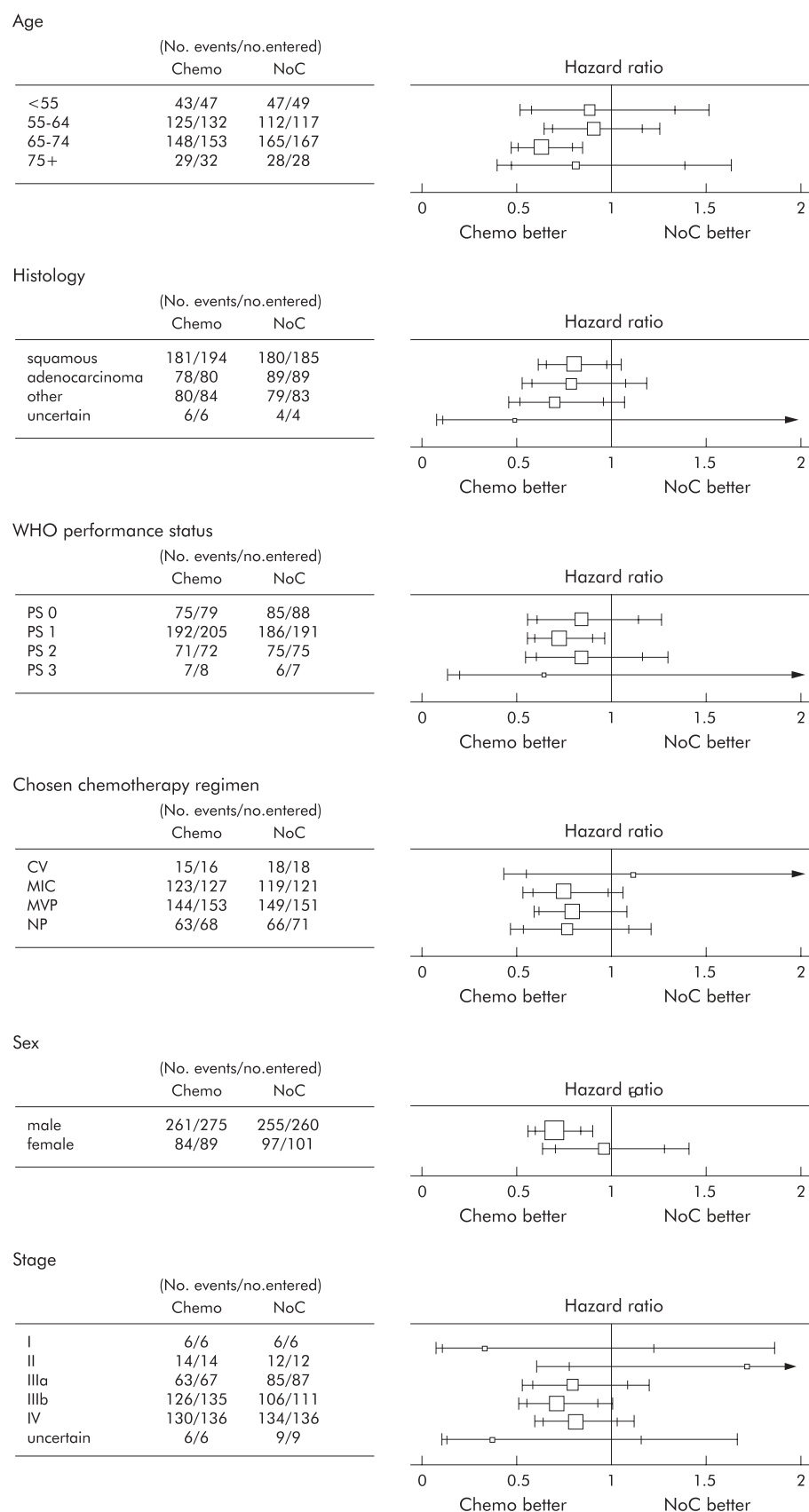


Figure 2 Hazard ratios and 95% and 99% confidence intervals for survival by subgroups.

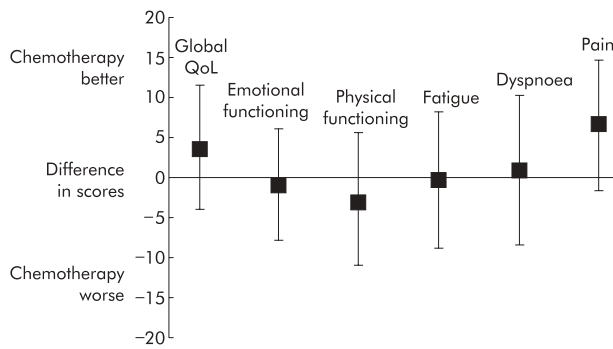


Figure 3 Differences (and 95% CIs) in the adjusted mean scores at 12 weeks for the primary and secondary quality of life end points. A large change has been defined as 10 points for global quality of life, 25 points for physical functioning, 7 for emotional functioning, and 20 for dyspnoea, fatigue and pain.⁵

that large positive or negative effects of chemotherapy on fatigue and dyspnoea at 12 weeks were all ruled out, but that the results for emotional functioning did not rule out the potential for large differences in either direction. For pain and physical functioning, some analyses indicated a large positive effect for chemotherapy but all ruled out large negative effects. Full details of the quality of life sub-study including comparisons of quality of life at other time points are presented elsewhere.⁷

Cost sub-study Patient sample

A total of 194 patients (99 C, 95 NoC) from eight of the highest recruiting centres were included in this sub-study. No significant differences were detected in baseline characteristics between the two treatment arms or between the 194 patients in this sample and the remaining 531 patients in the trial.

Costs

The net difference between the groups was approximately equal to the cost of the chemotherapy drugs themselves and administering them which, on average, totalled £1268. There was no difference between the groups in terms of all the other costs combined (C £4238, NoC £3718, $p = 0.3$) despite the fact that more patients in the NoC group received radiotherapy. As a result of the increased mean survival in the C group, the overall cost of treatment per week of life was the same (C £157, NoC £149). Chemotherapy in this trial was therefore deemed to be cost effective. Preliminary cost data

have been presented⁸ and full details will be published elsewhere.

DISCUSSION

With nearly 1400 patients recruited to all settings, the Big Lung Trial is one of the largest trials in NSCLC and the supportive care group, with 725 patients, is the largest study to investigate the value of chemotherapy in advanced disease. The trial has confirmed the survival benefit seen in the supportive care setting of the NSCLC meta-analysis¹ and has shown that, in patients with advanced NSCLC, cisplatin-based chemotherapy extends median survival by about 9 weeks and 1 and 2 year survival by 9% and 5%, respectively. It has also confirmed that the hazard ratio of about 0.75 is broadly consistent in all subgroups of patients studied (fig 2). Moreover, we have shown that chemotherapy generally does not have a negative impact on quality of life, and that the chemotherapy regimens used in this trial were cost effective.

The definition of supportive care was not defined in the protocol but was left to the discretion of the local clinician who could use radiotherapy if appropriate. In the event, 74% of patients allocated supportive care alone received radiotherapy, as did 47% of the patients allocated to receive chemotherapy.

Since the NSCLC meta-analysis,¹ a number of randomised trials comparing supportive care with or without platinum-based chemotherapy have been published. Cullen *et al*⁹ reported on 351 patients randomised to MIC chemotherapy or no chemotherapy, Thongprasert *et al*¹⁰ compared 287 patients in a three-arm trial, randomising patients to chemotherapy with MVP or ifosfamide/epirubicin/cisplatin or supportive care alone, and Helsing *et al*¹¹ studied 48 patients randomised to carboplatin and etoposide or supportive care. We are also aware of two other similar trials but the evidence from them is less reliable. The Ancona 2 trial¹² was a four-arm trial of 105 patients investigating the use of lonidamine with chemotherapy which was presented as an abstract in 1991 but not published, and a comparison of 78 patients receiving chemotherapy or no chemotherapy was reported by Anelli *et al*¹³ although it is not clear whether this was a randomised trial.

Survival

The relative survival benefit for cisplatin-based chemotherapy seen in the Big Lung Trial was entirely consistent with that reported in the NSCLC meta-analysis and the other randomised trials published since. Although this translates to a small absolute benefit in terms of median survival, equivalent to the time taken to give three cycles of chemotherapy, patients may be more persuaded by the fact that the probability of survival was increased by almost 50% at 1 year (from 20% to 29%) and doubled at 2 years (from 5% to 10%).

Table 5 Primary and secondary quality of life end points

	C		NoC	
	Baseline	12 weeks	Baseline	12 weeks
Global quality of life*	57.8	52.1	53.5	48.2
Emotional functioning*	70.5	68.6	64.8	69.3
Physical functioning*	66.8	51.0	60.0	53.5
Fatigue†	40.1	48.2	45.0	48.1
Dyspnoea†	39.1	46.5	48.2	47.6
Pain†	25.0	24.8	30.1	31.5

Data are mean standardised EORTC scores (range 0–100) at baseline and 12 weeks. The 12 week scores have been adjusted for baseline scores.

*In the functioning domains a high score represents good functioning.

†For individual symptoms, a high score represents increased severity.

The median survival in the supportive care only arm of the current trial appears significantly better than that reported in the other trials or the meta-analysis (5.7 months compared with 2.5–4.8 months), but this is almost certainly due to the fact that our design allowed the inclusion of patients with any stage of disease. Consequently, 56% of patients had stage III disease (median survival 6.7 months) and only 38% had stage IV disease (median survival 4.8 months) in the current trial.

Quality of life

The important contribution of our trial lies in the detailed assessment of quality of life. Of the eight trials in the supportive care setting included in the NSCLC meta-analysis, only two attempted to measure quality of life and both failed to report this aspect due to problems with compliance and data collection. Although quality of life has been assessed in some subsequent trials, the results of all of these can be criticised for a number of reasons. Cullen *et al*⁹ had an unbalanced patient sample (52 C, 32 NoC), used a trial-specific questionnaire, and compared the treatments using only the total quality of life score. Thongprasert *et al*¹⁰ used modified questionnaires and also only compared overall quality of life scores. Helsing *et al*¹¹ used standard questionnaires but only started with a total of 46 patients at baseline (20 C, 26 NoC) and by 24 weeks this number had reduced to only 16 (10 C, 6 NoC). Nevertheless, all these trials concluded that patients on chemotherapy reported a better quality of life than those not on chemotherapy. It is, of course, important to appreciate that a statistically significant improvement may not translate to a clinically significant difference.

On the other hand, the robust design of the quality of life aspect of the current trial ensured that standard questionnaires were used, the sample size was formally calculated to detect large differences in quality of life, there were predefined hypotheses, and a full analysis plan was written. Although no statistically significant differences were seen, the primary quality of life analyses did not rule out a significant positive effect of chemotherapy on quality of life, but it did confirm that in general chemotherapy did not have a large negative impact. The results implied that the side effects of chemotherapy (fatigue, reduced functioning) were balanced by the palliative effect on symptoms such as pain.

Cost

The analysis of costs indicated that chemotherapy was cost effective—that is, the extra cost was offset by the extra survival—and this is consistent with other studies which have compared the cost of chemotherapy with supportive care alone. While some authors^{14, 15} have suggested that the use of some chemotherapy regimens can actually reduce the overall cost compared with supportive care alone, most regimens are associated with increased costs which are generally considered acceptable. For example, Jaakkimainen *et al*¹⁴ calculated that the vindesine/cisplatin regimen was associated with an increased cost of \$15 000 (based on the cost in Canadian dollars in 1984) per life year saved, and Billingham *et al*¹⁶ calculated a cost increase of about £14 500 per life year saved with the use of the MIC regimen. In these studies the excess cost appeared to be mainly related to the number of hospital inpatient days. The regimens most used in the current trial (MIC and MVP) were usually administered on an inpatient basis and thus the use of outpatient regimens can be an effective way of reducing costs.¹⁵

Subgroups

There is no evidence from the current trial that any subgroup of patients, defined by age, sex, stage, cell type, performance

status, or chemotherapy regimen, benefited more or less from chemotherapy, although the numbers are small and the confidence intervals are wide. Although approximately 30% of patients in this trial were aged >70 years, elderly patients are generally under-represented in trials. However, the subgroup analyses suggest that age itself should not be a barrier to receiving chemotherapy.

Two recent reports^{17, 18} have suggested that patients with a baseline WHO PS of 2 or more do not benefit from chemotherapy and, in a large US trial examining four different chemotherapy regimens in advanced NSCLC,¹⁹ the accrual of PS 2 patients was discontinued due to a perceived high level of serious events. However, subsequent analysis of the PS 2 patients in the latter trial suggested that toxicity levels were in fact consistent with the PS 0/1 patients and that the poor outcome of the PS 2 patients (median survival about 4 months) was disease related rather than treatment related.²⁰ In addition, data from the NSCLC meta-analysis and now from the current trial do not suggest less benefit for PS 2 patients. In the current trial, although patients with PS 2/3 were reported as having more toxicity which, in turn, probably led to fewer cycles of chemotherapy being given and more delays and modifications of chemotherapy, they still had a similar relative survival benefit to patients with PS 0/1. It is important to remember that, although the relative benefit was similar for each subgroup, the absolute benefit is of course related to the expected survival. Using data from the current trial and based on an HR of 0.75, the absolute survival benefit for a subgroup of patients with a survival of 31 weeks (PS 0/1, stage III) would therefore be 11 weeks but, for a group with a survival of 9 weeks (PS 2/3 stage IV), the benefit would only be 3 weeks.

Treatment related deaths

Perhaps the major concern with chemotherapy is that 14 patients (4%) in the current trial were reported as having a treatment related death and a further five patients who were reported as dying from other causes were reclassified as treatment related deaths. Stephens *et al*²¹ defined a group of patients with small cell lung cancer at high risk of treatment related death as those with PS ≥ 2 , receiving four or more drugs, and a white cell count of $\geq 10\,000/\text{mm}^3$. However, because of the relatively small number of treatment related deaths in the current trial, there are insufficient data to be able to similarly identify patients with NSCLC at high risk before starting treatment. A large number of patients need to be studied so that in future “high risk” NSCLC patients can be identified and either not given chemotherapy or closely monitored.

Chemotherapy regimens

The current trial was not a randomised comparison of regimens. Clinicians could choose, on a patient by patient basis, any one of four possible regimens. There is evidence from randomised trials that the three-drug regimens MVP and MIC, which were received by 77% of patients in the chemotherapy arm of the current trial, are probably inferior in terms of survival and quality of life to two-drug regimens employing newer agents. For example, in preliminary reports Rudd *et al* found that the combination of gemcitabine and carboplatin conferred longer survival and better quality of life than MIC in patients with advanced NSCLC,²² and Melo *et al* reported that the combination of cisplatin with either gemcitabine or vinorelbine conferred longer survival than MVP.²³ Hence, there is reason to expect that the benefit for survival and quality of life from newer chemotherapy regimens may be greater than the 9 week median survival benefit suggested in the current trial without adverse effect on quality of life.

Patient acceptability

The survival benefit from cisplatin-based chemotherapy added to supportive care is now incontrovertible and the excess costs are considered acceptable. However, treatment decisions for individual patients may still be difficult as indicated by the results of a number of surveys. Of the patients identified in two London centres as eligible for the current trial and who gave a reason, 61 chose not to enter the trial as they did not want chemotherapy, compared with only eight who declined as they definitely did want chemotherapy.²⁴ The survey by Silvestri *et al*²⁵ indicated that patients may be more willing to accept chemotherapy for quality of life benefits than survival benefits. Brundage *et al*²⁶ reported that only about 50% of patients would choose chemotherapy over supportive care alone for the sort of survival benefit seen in this trial, and that it was not possible to predict—on the basis of factors such as age, sex, and education—what decisions patients would make. However, with newer drug regimens offering greater survival benefits, lower toxicity, and better quality of life,^{22–23} patients are likely to be increasingly willing to accept chemotherapy.

Conclusions

This large multicentre trial has confirmed the survival benefits of cisplatin-based chemotherapy in advanced NSCLC. It has shown that chemotherapy improves median and 1 year survival without a detrimental effect on quality of life and that the extra cost involved was offset by the longer survival. With increasing numbers of patients being offered chemotherapy, the additional information provided by this trial on quality of life should enable future patients and their clinicians to make more informed decisions about treatment in this difficult disease.

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