Pergamon

European Journal of Cancer, Vol. 34, No. 7, pp. 1036–1044, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(97)10122-8

Original Paper

Quality of Life and Survival in Patients with Advanced Non-small Cell Lung Cancer Receiving Supportive Care Plus Chemotherapy with Carboplatin and Etoposide or Supportive Care Only. A Multicentre Randomised Phase III Trial

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The aim of the present trial was to evaluate the effects of chemotherapy on the quality of life and survival of patients with advanced non-small cell lung cancer (NSCLC) (stage IIIB or IV). In a controlled multicentre trial, patients were randomised to receive supportive care only or supportive care plus chemotherapy. Chemotherapy consisted of intravenous (i.v.) carboplatin 300 mg/m^2 on day 1 and etoposide 120 mg/m^2 orally on days 1–5 every 4 weeks for a maximum of eight courses. Quality of life was measured at randomisation and prior to each treatment course and at corresponding 4-week intervals in the control arm, using the EORTC QLQ-C30 + LC13 questionnaire. 48 patients were randomised (supportive care 26, chemotherapy 22), being eligible for comparative analyses. Another 102 patients, 97 of which received chemotherapy, were subsequently included in the study on an individual treatment preference basis. Data from these patients were used for confirmative purposes. Patients in the chemotherapy group reported better overall physical functioning and symptom control compared with the supportive care group. Group differences were smaller within the psychosocial domain, although trends were seen in favour of the chemotherapy group. No significant differences were seen in favour of the supportive care group, except for hair loss. Median survival times were 29 weeks in the chemotherapy group versus 11 weeks in the supportive care group, and 1-year survival rates were 28% versus 8%. Quality of life and survival outcomes were similar in the randomised and non-randomised patients receiving chemotherapy. No treatment-related deaths occurred. In conclusion, treatment with carboplatin and etoposide can improve both the quality of life and the survival of patients with advanced NSCLC. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: non-small cell lung cancer, quality of life, best supportive care, chemotherapy, carboplatin, etoposide, survival
Eur J Cancer, Vol. 34, No. 7, pp. 1036–1044, 1998

INTRODUCTION

LONG-TERM survival in locoregionally advanced (stage IIIB) or metastatic non-small cell lung cancer (NSCLC) is rare and virtually independent of treatment modality. Randomised trials of cisplatin-based chemotherapy have demonstrated a modest improvement in median and 1-year survival when compared with best supportive care only [1]. The treatment, however, also has side-effects that may negatively affect the patients' well-being and the overall benefit from palliative

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Received 11 Jul. 1997; revised 20 Oct. 1997; accepted 17 Nov. 1997.
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chemotherapy in advanced NSCLC has remained controversial.

At the time of initiation of the present study, data on the quality of life of patients receiving chemotherapy for advanced NSCLC were sparse [2]. In an Italian randomised trial patients who received maintenance chemotherapy after two or three cycles of induction treatment reported better physical condition and, less surprisingly, experienced worse therapy tolerance compared with patients who did not have maintenance treatment [3]. Quality of life was evaluated by a three-item *ad hoc* questionnaire, which may have compromised the reliability of the results. In a Canadian randomised trial comparing supportive care with supportive care plus cisplatin-based chemotherapy in advanced NSCLC [4, 5], the aim of the investigators was to evaluate the patients' quality of life using the Functional Living Index—Cancer (FLIC) instrument. Owing to difficulties with questionnaire administration and patient compliance, follow-up on the patients self-reported quality of life data was insufficient. Since the survival benefit from chemotherapy was modest and the chemotherapy-related toxicity was regarded as rather severe, the authors concluded that palliative chemotherapy in advanced NSCLC should not be considered as standard therapy [5].

Partly in contrast to the above assumptions, a few chemotherapy trials in NSCLC employing well-documented instruments for quality of life evaluation have failed to demonstrate a clear relationship between treatment toxicity and patient self-reported psychosocial well-being [6, 7]. Furthermore, several trials have shown a correlation between tumour response and quality of life of NSCLC patients during chemotherapy [8, 9]. The data suggest that symptom control through delay of tumour progression may outweigh the negative impact of treatment toxicity on patients' well-being.

The primary aim of this randomised multicentre trial was to evaluate whether palliative platinum-based chemotherapy in advanced NSCLC has beneficial effects on patients' quality of life in comparison with supportive care only. For this purpose, we employed a modestly toxic outpatient treatment strategy which incorporated carboplatin combined with oral etoposide and the EORTC quality of life instrument as an internationally well-documented [10] and sufficiently comprehensive assessment method. Survival was considered as a secondary treatment end-point.

PATIENTS AND METHODS

Study design

The study was conducted as a controlled, randomised, multicentre phase III trial. Eligible patients were randomised to receive best supportive care (BSC) or BSC plus chemotherapy (CT) with carboplatin and oral etoposide for a maximum of eight cycles. The primary outcome variable was quality of life, measured as the change from baseline to follow-up.

The study was approved by the Ethics Committees of all participating centres and carried out according to the Helsinki declaration.

One year after commencement of the trial, it became obvious that some of the participating centres were unable to obtain patients' consent for the randomisation. It was then decided that those centres would have the option to continue enrolling patients on a treatment preference basis, employing the same eligibility criteria, treatment plan and evaluation schedule as for the randomised patients. The non-randomised patients would be used for confirmative purposes.

Patients

In the original protocol, patients with histologically or cytologically proven NSCLC, stage IIIB or IV were eligible. Two years after the commencement of the study, only stage IV was accepted due to new reports suggesting that combined radiochemotherapy in locally advanced disease may improve long-term survival. Other eligibility criteria included: measurable or evaluable disease, no prior chemotherapy, no prior malignancy, except for basal cell cancer of the skin or cancer *in situ* of the cervix, age less than 75 years, WHO performance status ≤ 2, haemoglobin ≥ 90 g/l, white blood cell count $\geq 3.5\times10^9$/l, platelet count $\geq 120\times10^9$/l, S-creatinine ≤ 120 μmol/l or creatinine clearance ≥ 60 ml/min and informed consent.

Staging and clinical monitoring

Minimum staging procedures included blood chemistry, chest X-ray and a computerised tomography (CT) scan or ultrasound of the liver if the patient did not have proven metastasis elsewhere. Further screening for metastases was optional. Blood cell counts, blood chemistry, performance status assessment and chest X-ray were repeated prior to every new treatment cycle in the chemotherapy arm and at corresponding 4 week intervals in the control arm.

Treatment

Chemotherapy consisted of intravenous (i.v.) carboplatin (Paraplatin®, Bristol-Myers Squibb) 300 mg/m^2 on day 1 and etoposide (Vepesid®, Bristol-Myers Squibb) 120 mg/m^2 daily orally on days 1–5. This regimen was repeated every 4 weeks for a maximum of eight cycles. Chemotherapy was discontinued in the case of tumour progression, a deterioration of performance status to 3 or worse, intolerable toxicity, serious concomitant morbidity, or on the patient's request. The use of anti-emetics, such as bethametasone and a 5-HT$_3$ receptor blocker, was recommended.

Best palliative care was given at the discretion of the investigators, and included the option of palliative radiotherapy, opioid analgesics and psychosocial support.

Quality of life assessment

Quality of life was assessed by the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) and Lung Cancer Questionnaire module (QLQ-LC13). The QLQ-C30 was designed for use in cancer patients participating in clinical trials [10]. It incorporates five multi-item functioning scales, a global quality of life scale and an array of single- or multi-item measures of symptoms that are frequently experienced by cancer patients in general. The QLQ-LC13, which was designed to supplement the core questionnaire [11], addresses specific symptoms associated with lung cancer and its standard treatment, which are either not incorporated or are only covered in general terms by the core questionnaire.

Based on assumptions of clinically relevant inter-scale correlations, which were also confirmed by a factor analysis of the total study population (data not shown), two summary indices corresponding to the physical and psychosocial domains of quality of life were formed. The physical index was calculated as the mean score of the physical and role

functioning scales and the fatigue scale (the fatigue scale was reversed to match the polarity of the functioning scales). The psychosocial index was calculated as the mean score of the emotional, cognitive and social functioning scales. The purpose of creating these indices was to facilitate the evaluation of quality of life by reducing the number of dependent variables. It should, however, be pointed out that the index construction is not included in the official scoring guidelines for the EORTC instrument.

Quality of life was measured at randomisation and following each 4-week course of treatment in the chemotherapy arm, and at corresponding 4-week intervals in the best supportive care arm. A measurement 'window' of ± 2 weeks was allowed. Thus, measurements within 2 weeks following randomisation were regarded as baseline measurements, measurements during weeks 3–6 were regarded as 4-week follow-up measurements, etc.

Statistical analysis

Significant tests of group differences referring to quality of life variables were carried out by means of non-parametric measures. However, for ease of presentation, group scores in the results are generally referred to as mean values. The effect of treatment on change over time was evaluated by group comparisons of ranks of individual score differences from randomisation to each follow-up assessment, using the Mann–Whitney *U* test. In addition, the median of score differences from baseline to follow-up measurements was calculated for each variable and individual and used as a summary measure for significance analysis by means of the Mann–Whitney *U* test. Imputation of missing data due to patient attrition was not carried out. The Kaplan–Meier method and logrank test were used for survival analysis [12]. All *P* values refer to two-sided tests. The statistical significance level was set to 5%.

RESULTS

Patient characteristics

Between December 1990 and September 1995, a total of 151 patients were enrolled into the study, with a median follow-up time of 40 months (September 1996). 49 patients were randomised to receive supportive care only or supportive care plus chemotherapy, referred to as the BSC-R and CT-R groups, respectively. 1 patient who was randomised to the BSC-R group withdrew his consent and did not participate in subsequent quality of life evaluations (Figure 1).

Pretreatment characteristics of the study population are shown in Table 1. The two groups of randomised patients were similar with regard to age, performance status and distribution of histological tumour types, of which adenocarcinoma was the most frequent. The proportion of males was somewhat higher in the BSC-R group than in the CT-R group, but the difference was not statistically significant ($P = 0.3$). The reported frequency of liver metastases was higher in the BSC-R group, but in 18 of 48 randomised patients a CT scan or ultrasound of the liver was not performed.

102 patients were enrolled and allocated to treatment on a preference basis rather than by randomisation. Of these, 97 chose to have chemotherapy (CT-nR), and only 5 preferred a palliative care without chemotherapy (BSC-nR). As stated above, the non-randomised patients were used solely for confirmative purposes and they were not included in comparative analyses and significant tests, unless explicitly stated.

Table 1. *Baseline characteristics of* 48 *randomised and* 102 *non-randomised patients with advanced non-small cell lung cancer*

	CT-R $n = 22$ (%)	BSC-R $n = 26$ (%)	CT-nR $n = 97$ (%)	BSC-nR $n = 5$ (%)	All $n = 150$ (%)
Gender					
Male	12 (55)	18 (69)	55 (57)	3 (60)	85 (59)
Female	10 (45)	8 (31)	42 (43)	2 (40)	62 (41)
Age (years)					
Median	61	64.5	64	72	64
Range	36–72	44–78	37–78	66-78	36–78
WHO performance status					
0	4 (18)	5 (19)	15 (16)	1 (20)	25 (17)
1	11 (50)	11 (42)	47 (48)	2 (40)	71 (47)
2	7 (32)	10 (38)	35 (36)	2 (40)	54 (36)
Histology					
Adenocarcinoma	15 (68)	17 (65)	53 (55)	4 (80)	89 (60)
Large cell	3 (14)	4 (15)	16 (16)	0 (0)	23 (15)
Squamous cell	4 (18)	5 (19)	27 (28)	1 (20)	37 (24)
Adenosquamous	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Stage					
IIIb	2 (9)	3 (12)	8 (8)	0 (0)	13 (9)
IV	20 (91)	23 (88)	89 (92)	5 (100)	137 (91)
Prior treatment					
Surgery	2 (9)	2 (8)	12 (12)	0 (0)	16 (11)
Radiotherapy	2 (9)	1 (4)	13 (13)	1 (20)	17 (11)
Liver metastases					
Present	1 (5)	5 (19)	12 (12)	2 (40)	20 (13)
Not present	18 (82)	15 (58)	74 (76)	2 (40)	109 (73)
Unknown	3 (13)	6 (23)	11 (11)	1 (20)	21 (14)

CT-R, randomised chemotherapy group; BSC-R, randomised supportive care group; CT-nR, non-randomised chemotherapy group; BSC-nR, non-randomised supportive care group.

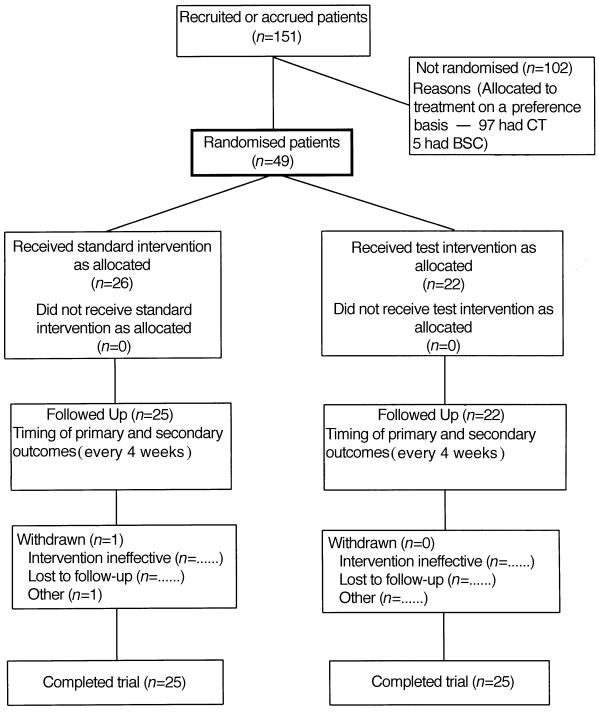

Figure 1. Flow chart of the progress of patients through the trial. (Adapted from Begg C, Cho M, Eastwood S, *et al.* Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996, 276, 637–639.)

Chemotherapy

Figure 2 shows the number of chemotherapy courses given in both randomised and non-randomised patients. Eighteen per cent of patients in the CT-R group and 24% in the CT-nR group completed the eight planned treatment courses, while approximately the same proportion of patients (15–22%) received only one treatment course. The median number of completed treatment courses was 4 in both groups.

Dose intensity was calculated as the quotient of the intended dose for each drug and treatment course multiplied by the number of courses given and divided by the total dose given. In the CT-R group, 71% of patients received full doses of both drugs at every treatment given, while no patient had a dose intensity less than 75%. In the CT-nR group, full doses of carboplatin and etoposide were given to 29 and 46%, respectively, and in 10% of patients, the dose intensity was < 75%.

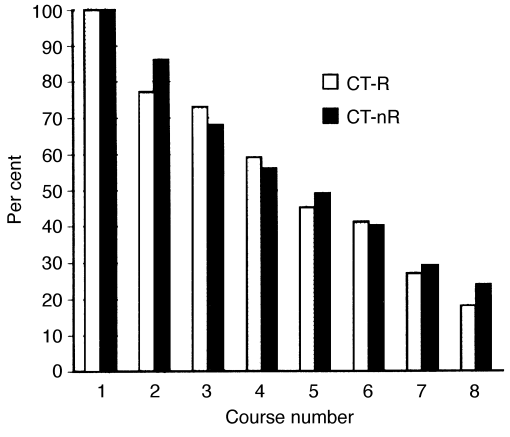

Figure 2. The number of chemotherapy courses given to randomised and non-randomised patients.

Haematological toxicity was mild. In the CT-R group, there was no case of grade 4 leucopenia after the first treatment course, while 3 patients (14%) had grade 4 thrombocytopenia. In the CT-nR group, the corresponding proportions with a grade 4 leucopenia or thrombocytopenia were 5 and 16%, respectively. 3 patients (14%) in the CT-R group and 2 patients (2%) in the CT-nR group stopped treatment because of haematological toxicity and 1 patient in each group stopped treatment because of other toxicity. No treatment-related death occurred.

All patients received anti-emetic treatment with bethametasone i.v. and one 5-HT_3 receptor blocker. During the quality of life follow-up, 6 (23%) patients in the BSC-R group, 2 (9%) patients in the CT-R group and 18 (18%) of the non-randomised patients were treated with palliative radiation.

Survival and time to progression

Survival curves are shown in Figure 3. The median survival was 29 weeks in the CT-R group (range 6–205+ weeks) and 11 weeks in the BSC-R group (range 4–90 weeks). Overall survival was superior in the CT-R group ($P = 0.003$; logrank test). The probability of 1-year survival was 28% in the CT-R group compared with 8% in the BSC-R group. 4 patients in the CT-R group survived more than 2 years.

The patients in the CT-nR group (included in Figure 3 for illustration) had a median survival time of 30 weeks and a 1-year survival of 22%. This was similar to the CT-R group. 2 patients were alive at 2 years.

The time to progression, calculated from randomisation, is shown in Figure 4. Patients in the CT-R group had a significantly longer time to the first recognised tumour progression than patients in the BSC-R group ($P < 0.0001$), while the curves were similar in the CT-R and CT-nR groups.

Patients who received chemotherapy (CT-R and CT-nR groups taken together) and who had a pretreatment performance status of 0 had a better overall survival in comparison with patients with performance status of 1 or 2 ($P = 0.017$ and $P = 0.007$, respectively).

Quality of life

Baseline quality of life assessment was completed by 46 of 48 randomised patients who accepted their treatment allocation.

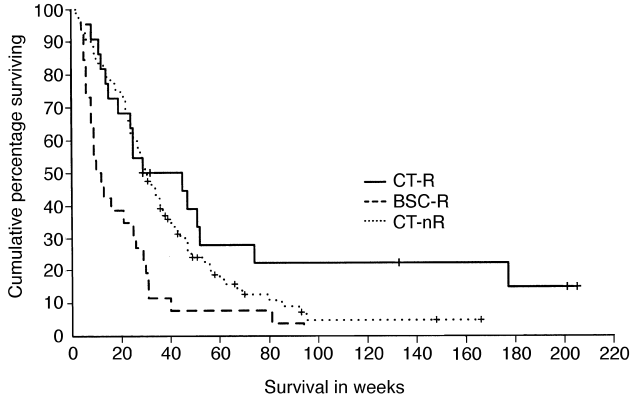

Figure 3. Survival of randomised patients receiving chemotherapy (CT-R) or supportive care only (BSC-R) and of non-randomised patients receiving chemotherapy (CT-nR). The survival was superior in the CT-R group compared with the BSC-R group ($P = 0.003$; logrank test).

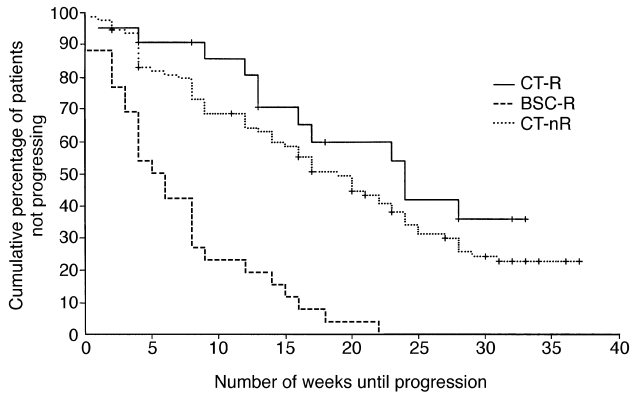

Figure 4. Time to progression in randomised patients receiving chemotherapy (CT-R) or supportive care only (BSC-R). The progression-free survival was significantly longer in the CT-R group ($P < 0.0001$). For illustration, the curve representing progression-free survival of non-randomised patients receiving chemotherapy (CT-nR) is included in the figure.

The 2 missing patients, both randomised to receive chemotherapy, completed their first quality of life assessments by 4 and 12 weeks, respectively.

Mean scores for functioning and symptom measures at baseline are shown in Table 2. With the exception of pain, where patients in the CT-R group reported somewhat higher levels (38.4 versus 26.3, $P = 0.24$), only small score differences were seen between the two randomised study groups before onset of treatment. For illustration, baseline scores of non-randomised patients are included in Table 2.

Follow-up assessments at 4, 8, 12, 16, 20 and 24 weeks were completed by 39 (BSC-R 21, CT-R 18), 30 (BSC-R 15, CT-R 15), 25 (BSC-R 10, CT-R 15), 22 (BSC-R 9, CT-R 13), 22 (BSC-R 9, CT-R 13) and 16 (BSC-R 6, CT-R 10) patients, respectively. In 32 cases (BSC-R 20, CT-R 12), quality of life assessments were discontinued before 24 weeks due to tumour progression, general deterioration or death. The time span from the end of quality of life assessment and death in this group with early discontinuation varied between 2 and 75 days, with a median of 23 days in the CT-R group and 20 days in the BSC group.

Mean functioning and global quality of life score changes from baseline are shown in Table 3. At every follow-up measurement, the mean physical functioning score was reduced by more than 15 score points in the BSC-R group, while the mean score of the CT-R group did not change much over time. While the group difference was significant only at 20 weeks when each follow-up assessment was analysed separately, the rank of median physical functioning score changes over the whole period of 24 weeks was significantly higher (i.e. better) in the CT-R group ($P = 0.0096$).

A similar trend was seen in social functioning and global quality of life. The social functioning score showed a constant deterioration in the BSC-R group which was significantly different from the CT-R group at 8 and 20 weeks. Moreover, the rank of median score changes over the 24-week period was significantly higher (i.e. better) in the CT-R group ($P = 0.032$). With the exception of the assessment at 24 weeks, the mean global quality of life score changes in the CT-R group were positive, while in the BSC-R group a consistently negative trend was seen. Over the whole 24-week period, there was a non-significant group difference in favour of the CT-R group ($P = 0.063$).

For emotional, cognitive and role functioning, group differences were smaller and less consistent and the comparison of ranks of median score changes over 24 weeks non-significant ($P = 0.15$, $P = 0.42$, and $P = 0.61$, respectively).

Corresponding results referring to the symptom measures are shown in Table 4. For a number of symptoms (i.e. fatigue, pain, appetite loss, dyspnoea, sleep disturbance, constipation and coughing), significant group differences of score changes in favour of the CT-R group were seen at one, two or three follow-up assessments. In contrast, no significant

Table 2. Mean baseline quality of life scores (functioning and disease-related symptom measures) in 46 randomised and 99 non-randomised study patients who were evaluable for quality of life

	BSC-R ($n = 26$) mean ± S.D.	CT-R ($n = 20$) mean ± S.D.	BSC/CT-nR ($n = 99$) mean ± S.D.
Functioning scales			
Physical	63.1 ± 29.8	59.8 ± 29.6	65.5 ± 25.2
Role	48.1 ± 38.7	60.0 ± 34.8	55.7 ± 39.4
Emotional	71.2 ± 20.5	65.4 ± 23.4	64.3 ± 22.2
Cognitive	80.8 ± 23.8	80.9 ± 21.1	83.8 ± 19.5
Social	68.0 ± 30.7	68.5 ± 30.9	72.1 ± 28.8
Global quality of life	53.0 ± 20.5	51.6 ± 27.9	55.5 ± 20.7
Symptom scales/items			
Fatigue	53.4 ± 25.1	48.1 ± 28.6	42.5 ± 23.5
Pain	26.1 ± 28.3	38.4 ± 34.6	31.0 ± 29.1
Appetite loss	24.3 ± 33.4	28.3 ± 37.9	23.8 ± 32.1
Nausea/vomiting	12.2 ± 23.9	8.4 ± 22.6	9.3 ± 16.0
Dyspnoea	50.1 ± 21.9	48.3 ± 35.1	29.7 ± 22.5
Sleep disturbance	30.7 ± 28.2	28.4 ± 33.0	35.7 ± 29.7
Constipation	16.7 ± 25.4	30.0 ± 40.3	16.6 ± 28.8
Diarrhoea	2.5 ± 9.0	3.3 ± 10.2	8.0 ± 17.8
Coughing	48.7 ± 33.1	38.3 ± 27.2	38.7 ± 28.7
Haemoptysis	3.8 ± 14.4	1.7 ± 7.4	4.0 ± 12.8
Chest pain	23.0 ± 24.6	25.0 ± 35.7	22.1 ± 27.4

BSC-R, randomised supportive care group; CT-R, randomised chemotherapy group; BSC/CT-nR, merged, non-randomised supportive care and chemotherapy groups; S.D., standard deviation.

Table 3. Mean functioning score changes from baseline in randomised patients

Domain	Treatment	Mean score change from baseline (ΔT0)*					
		4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	24 weeks
Physical	BSC-R	−17.4	−17.3	−20.0	−16.7	−37.8	−23.3
	CT-R	−5.3	−2.7	−0.7	−2.3	−4.2	−3.5
	$P_{\Delta T0}$†	0.080	0.21	0.12	0.061	0.025	0.16
Role	BSC-R	−9.5	−20.0	−15.0	−22.2	−50.0	−25.0
	CT-R	−11.1	−6.7	−10.7	−11.5	−7.7	−15.0
	$P_{\Delta T0}$	0.95	0.34	0.65	0.42	0.054	0.57
Emotional	BSC-R	−2.1	2.0	10.9	−1.8	−4.6	0
	CT-R	1.4	14.3	7.8	15.4	11.5	12.6
	$P_{\Delta T0}$	0.80	0.14	0.80	0.17	0.099	0.21
Cognitive	BSC-R	−3.2	−2.2	11.7	−5.5	−24.1	2.8
	CT-R	−4.7	−2.2	−4.4	−3.9	−10.3	6.7
	$P_{\Delta T0}$	0.75	0.81	0.046	0.60	0.11	0.81
Social	BSC-R	−4.2	−17.7	−6.8	−12.9	−35.1	−22.0
	CT-R	5.8	13.1	4.8	0.1	2.8	5.3
	$P_{\Delta T0}$	0.15	0.0022	0.089	0.21	0.0092	0.064
Global quality of life	BSC-R	−8.0	−6.9	−0.7	−14.8	−25.9	−8.3
	CT-R	2.4	7.3	3.9	4.5	1.9	−2.4
	$P_{\Delta T0}$	0.099	0.11	0.84	0.075	0.020	0.44

BSC-R, randomised supportive care group; CT-R, randomised chemotherapy group.
*Positive numbers indicate a higher functioning score at follow-up (i.e. improvement), while negative numbers indicate a reduction in the mean score (i.e. deterioration). †*P* values refer to Mann–Whitney *U* test of the ranks of score changes by treatment group.

Table 4. Mean disease-related symptom score changes from baseline in randomised patients

Domain	Treatment	Mean score change from baseline (ΔT0)*					
		4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	24 weeks
Fatigue	BSC-R	8.9	15.0	3.4	10.0	25.9	11.3
	CT-R	5.8	−8.6	−5.5	−6.4	−3.5	−2.7
	$P_{\Delta T0}$†	0.96	0.0058	0.59	0.20	0.066	0.42
Pain	BSC-R	18.3	6.7	3.4	14.9	26.0	5.5
	CT-R	−14.9	−10.1	−10.1	−1.3	−6.4	−3.2
	$P_{\Delta T0}$	0.0007	0.095	0.24	0.15	0.054	0.22
Appetite loss	BSC-R	11.1	22.3	−6.7	14.9	37.1	0.0
	CT-R	−1.9	−13.3	−2.1	−5.1	7.8	3.4
	$P_{\Delta T0}$	0.18	0.011	0.40	0.21	0.11	0.69
Nausea and vomiting	BSC-R	5.5	10.1	3.4	1.8	16.7	5.5
	CT-R	3.7	0.0	−10.1	2.5	7.6	8.3
	$P_{\Delta T0}$	0.52	0.053	0.24	0.78	0.43	0.90
Dyspnoea‡	BSC-R	7.0	1.6	−1.1	20.0	18.6	11.2
	CT-R	−6.2	−1.5	−2.7	−3.6	0.2	−1.9
	$P_{\Delta T0}$	0.041	0.45	0.78	0.027	0.11	0.19
Sleep disturbance	BSC-R	14.3	9.0	−1.1	11.0	29.7	−0.2
	CT-R	−5.6	4.5	−6.7	5.2	−2.5	−10.0
	$P_{\Delta T0}$	0.049	0.55	0.047	0.50	0.022	0.57
Constipation	BSC-R	−1.6	11.1	−0.1	18.4	22.1	16.5
	CT-R	−11.1	−17.8	−11.1	0.0	5.2	0.0
	$P_{\Delta T0}$	0.47	0.013	0.16	0.17	0.17	0.017
Diarrhoea	BSC-R	4.8	0.0	3.7	−3.7	14.8	11.0
	CT-R	3.7	2.2	2.3	−2.5	7.7	−3.3
	$P_{\Delta T0}$	0.96	0.55	0.50	0.79	0.73	0.13
Coughing	BSC-R	6.4	6.8	−3.2	7.7	11.2	−16.5
	CT-R	−11.2	−11.1	−2.2	−10.3	−20.6	−20.0
	$P_{\Delta T0}$	0.028	0.071	0.95	0.12	0.027	0.49

BSC-R, randomised supportive care group; CT-R, randomised chemotherapy group.
*Positive numbers indicate a higher symptom score at follow-up (i.e. deterioration), while negative numbers indicate a reduction in the mean score (i.e. improvement). †*P* values refer to Mann–Whitney *U* test of the ranks of score changes by treatment group. ‡The dyspnoea measure refers to the three-item dyspnoea scale in the QLQ-LC13.

Table 5. Mean treatment-related symptom score changes from baseline in randomised patients

Domain	Treatment	Mean score change from baseline (ΔT0)*					
		4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	24 weeks
Sore mouth	BSC-R	1.6	0.0	0.0	0.0	0.0	11.0
	CT-R	12.9	−2.3	−0.1	0.0	2.5	3.3
	$P_{\Delta T0}$†	0.34	0.55	0.97	1.0	0.41	0.26
Dysphagia	BSC-R	11.0	13.3	0.0	7.3	7.3	11.0
	CT-R	5.6	−4.4	2.2	−2.8	5.2	0.0
	$P_{\Delta T0}$	0.34	0.015	0.41	0.070	0.77	0.059
Peripheral neuropathy	BSC-R	4.7	−6.7	3.2	0.0	−3.6	16.5
	CT-R	12.9	11.1	6.7	7.7	10.2	3.3
	$P_{\Delta T0}$	0.55	0.028	0.94	0.41	0.43	0.083
Hair loss	BSC-R	0.0	−2.3	6.7	7.4	−7.4	16.7
	CT-R	74.1	60.0	60.0	47.3	41.0	60.0
	$P_{\Delta T0}$	< 0.0001	< 0.0001	0.0023	0.045	0.0027	0.073

BSC-R, randomised supportive care group; CT-R, randomised chemotherapy group.
*Positive numbers indicate a higher symptom score at follow-up (i.e. deterioration), while negative numbers indicate a reduction in the mean score (i.e. improvement). †*P* values refer to Mann–Whitney *U* test of the ranks of score changes by treatment group.

differences in favour of the BSC-R group were seen. The rank of median score changes over 24 weeks differed significantly between the groups for pain ($P = 0.0042$), sleep disturbance ($P = 0.032$) and dyspnoea ($P = 0.042$) and was borderline for fatigue ($P = 0.062$), in all cases in favour of the CT-R group. With regard to site-specific pain, no significant group differences were recorded (data not shown).

In Table 5, data on symptoms associated primarily with treatment side-effects are shown. Hair loss was significantly more frequently reported by patients in the CT-R group, as was expected. Peripheral neuropathy was reported somewhat more frequently in the CT-R group, but the group difference was significant only at 8 weeks. Patients' reports on dysphagia and problems with a sore mouth showed a less consistent pattern.

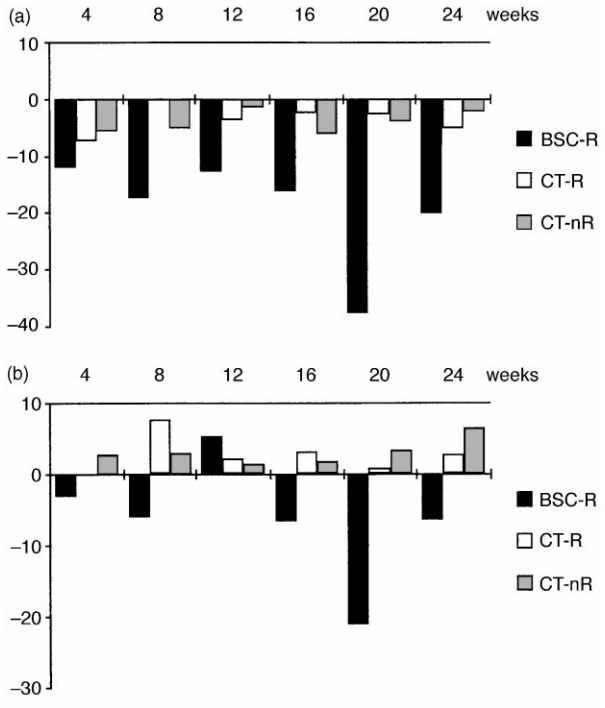

Figure 5. Change of (a) physical index and (b) psychological index from baseline to each follow-up assessment. Negative delta scores indicate a deterioration. BSC-R, randomised best supportive care; CT-R, randomised chemotherapy; CT-nR, non-randomised chemotherapy.

Score differences from baseline for the physical and psychosocial indices are shown in Figure 5. This figure also includes data from the CT-nR group (non-randomised study patients receiving chemotherapy) for illustration and confirmation of the results from the comparison of randomised patients. In the BSC-R group, there was a consistent reduction (i.e. deterioration) of the physical index below 10 score points from the baseline index score, while, in both CT groups (randomised and non-randomised), index score changes were smaller. A comparison of median index score changes over the whole 24-week period in BSC-R and CT-R patients showed a significant difference in favour of the CT-R group ($P = 0.047$). In both randomised and non-randomised CT patients, the psychosocial index increased (i.e. improved) marginally at all follow-up measurements, while the pattern was less favourable in the BSC-R group, with several index score reductions from baseline (i.e. deteriorations). The difference, however, between BSC-R and CT-R patients over the 24-week period was non-significant ($P = 0.10$).

DISCUSSION

The results of the present trial suggest favourable effects of chemotherapy with carboplatin and etoposide on both the survival and the quality of life of patients with advanced NSCLC. Since the numbers of randomised and evaluable patients were small, which increases the risk of random effects, the results have to be interpreted with some caution. The overall pattern of results is, however, unequivocal and the outcome does not suggest that chemotherapy for advanced NSCLC would have a significantly negative impact on the quality of life.

The major problem of the present trial was to obtain patients' consent for randomisation. Several factors may have contributed to the difficulties. Firstly, the content of the supportive treatment in the control arm may not have been sufficiently well defined to represent an acceptable alternative to chemotherapy. In the study protocol, supportive treatment was defined as measures taken against disease-related symptoms, and included the option of palliative radiotherapy.

These treatment options, however, were not defined in detail, and the interpretation of the protocol guidelines may have varied across centres. Secondly, the variation in patient accrual across participating centres may have mirrored slightly different views among the investigators on the value of chemotherapy in advanced NSCLC. Recommendations from consensus meetings in Sweden have been very restrictive concerning the use of palliative chemotherapy outside the context of clinical trials. During the trial, increasing evidence of short-term survival benefit from platinum-based chemotherapy emerged [13–15], which may have had an impact on the information given to patients concerning the potential treatment outcome. Finally, the chemotherapy regimen used was anticipated to be only moderately toxic and during the study, new effective anti-emetics became available. Hence, the potential side-effects of chemotherapy probably did not deter a majority of the patients.

The multidimensional nature of quality of life as an outcome measure, in addition to the small number of patients, creates potential problems with random effects and mass significance. One way of handling these problems is to define one or two measures related to the core dimensions of quality of life as primary outcome variables. The construction of summary indices was an attempt in this direction. Together with the global quality of life measure, they would cover and distinguish the core domains of health-related quality of life. In the present trial, these measures pointed to a less favourable outcome in patients who did not receive chemotherapy, at least with regard to the physical domain and probably also in global quality of life.

Another approach is to focus on response patterns, rather than specific measures. Clinically important treatment effects would then be mirrored in several related measures, or at several time points in serial assessments of the same variable. Moreover, conflicting results within the same domain should not occur if positive results are to be considered clinically relevant. In the present trial, the pattern of responses clearly pointed to a less favourable outcome in the BSC-R group with regard to physical and social function and symptom control, while the response pattern within the psychological dimension was less consistent. The validity of the observations is supported by the response pattern of the numerically larger sample of non-randomised patients receiving chemotherapy.

The possible benefit from chemotherapy with respect to quality of life is probably related to the delay of tumour progression. Previous trials in NSCLC [8, 9, 16], as well as in small cell lung cancer [17], have identified tumour progression as one of the most important explanatory factors for deterioration of quality of life. In contrast, the grade of objective tumour response does not seem to influence the patients' subjective experience of well-being. Thus, from a palliative point of view, chemotherapy effects both in terms of stable disease and tumour remissions seem to be important clinical treatment goals.

Data from comparative chemotherapy trials in NSCLC comprising a supportive care control arm are still sparse. Apart from the previously cited studies [3–5], a more recent trial [18] showed that chemotherapy resulted in a more favourable outcome in comparison with supportive care only, both with regard to survival and in terms of quality of life as measured by modified versions of the FLIC questionnaire and the Quality-of-Life Index. Although a different set of assessment tools were used, these results are consistent with our findings and support the hypothesis that chemotherapy may have a clinically important role in the palliative treatment of NSCLC.

The observed effects of chemotherapy on survival were somewhat larger than would have been expected from previous trials comparing platinum-based chemotherapy with best supportive care [1, 19]. The survival in the CT-R group was well within the range of previous findings in similar phase III trials [5, 20–25], which have shown median survival times between 22 and 34 weeks and 1-year survival rates varying around 26% in patients receiving chemotherapy. The survival in the control arm, however, was in the lower range of previously reported results in patients receiving supportive care without chemotherapy, which has shown a median survival time of 10–21 weeks and a 1-year survival rate averaging 16%. It is, therefore, possible that the effects of chemotherapy on survival in the present study are somewhat overestimated due to an unexpectedly poor survival in the control arm, possibly due to an imbalance with regard to some prognostic factors, such as the frequency of liver metastases. The length of survival in the chemotherapy arm is less likely to be overestimated, an assumption that is further supported by the survival outcome of non-randomised patients receiving chemotherapy in the confirmative part of the study.

In the light of the survival differences, the results pertaining to quality of life become even more interesting. The patients who completed follow-up assessments were the ones that were still able to comply with the assessment procedures, while patients who deteriorated or died were not assessed. Since the attrition due to deterioration and death was larger in the control arm, patients receiving supportive care only were more selected and less representative of the baseline study population than were patients in the chemotherapy arm. Consequently, the difference between the groups with regard to change of quality of life would have been even more significant if the analysis had incorporated a method for imputation of missing data due to death. It is not likely, therefore, that the observed treatment effects on changes of quality of life are overestimated, while it is quite possible that they are in fact underestimated since patient attrition was not included in the quality of life equation.

Cisplatin has for many years constituted a basic element of chemotherapy in NSCLC [26] and cisplatin–etoposide has been one of the most frequently used combination regimens in NSCLC. In palliative settings, the subjective toxicity profile of cisplatin, including nausea and vomiting, neuro- and nephrotoxicity, may sometimes be experienced as unacceptable. Carboplatin has proven activity in NSCLC and a more favourable subjective toxicity profile [27]. In an EORTC study comparing the two platinum compounds in combination with etoposide, no differences were shown with regard to the effects on survival [28]. These data, in addition to the ease of administration in outpatient settings, was the major reason for choosing the carboplatin–etoposide regimen for the experimental arm in the present study.

In conclusion, we found that patients with advanced and incurable NSCLC who were receiving outpatient chemotherapy with carboplatin and etoposide had a better 1-year and median survival and during a period of 4–24 weeks a less unfavourable impact of the disease on the quality of life in comparison with patients who did not receive chemotherapy. We believe that our results lend support to the carboplatin–

etoposide regimen as being both effective and well tolerated when used as a palliative treatment for advanced NSCLC.

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Acknowledgement—The study was supported by an educational grant from Bristol-Myers Squibb, Sweden.