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Chemotherapy improves low performance status lung cancer patients

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ABSTRACT: The aim of the present study was to determine the potential benefit of conventional cisplatin-based chemotherapy on patients with advanced nonsmall cell lung cancer (NSCLC) and poor performance status (PS), defined as 60–70 on the Karnofsky scale.

Retrospective analysis was carried out of a randomised trial performed in advanced NSCLC where 485 patients received three courses of gemcitabine+ifosfamide+cisplatin induction chemotherapy.

Of the patients, 80% had good PS (Karnofsky 80–100) and 20% poor PS. Response rates were 38 and 28%, respectively. Clinical improvement, defined as achieving a good PS during chemotherapy, was observed overall in 25% of the poor PS patients, with rates of 38, 20 and 14%, respectively, in case of response, no change and progression. PS improved more quickly in the responders. Survival of patients with poor PS was significantly worse, but survival of responders was similar, irrespective of the initial poor or good PS. Although nonfatal toxicity was almost similar, there were more toxic deaths (including vascular and cardiac fatalities) in the poor PS patients (9.2 *versus* 2.1%).

In conclusion, combination chemotherapy is associated with clinical improvement in a substantial number of patients with advanced nonsmall cell lung cancer of poor performance status.

KEYWORDS: Cancer research, chemotherapy, nonsmall cell lung cancer, performance status

Performance status (PS) is a strong independent prognostic factor for survival of patients with advanced nonsmall cell lung cancer (NSCLC) [1–4]. Two scales are commonly used to grade PS for lung cancer: the Eastern Cooperative Oncology Group (ECOG) scale (0–5) and the Karnofsky scale (100–0). Usually, patients selected for trials should have a PS of $\geqslant$60 on the Karnofsky scale or $\leqslant$2 on the ECOG scale. ECOG PS 2 and Karnofsky PS 60–70 are considered as equivalent [5], and they are associated with a poorer prognosis.

In 1997, the data monitoring committee of ECOG study 01599 compared four platinum-based chemotherapy regimens [6] and observed a substantial rate of toxicity in patients with a PS of 2 and, in August 1997, accrual of patients with PS 2 was discontinued because of excessive toxicity and a high rate of toxic deaths (five (7.6%) out of 66) [7]. The authors suggested that because of excessive toxicity and shorter survival, therapy specifically tailored for PS 2 patients needed to be explored and that PS 2 has to be a criterion of exclusion for trials enrolling patients with good performance index. This proposal was implemented in the 2003 American Society of Clinical Oncology (ASCO) guidelines [8] and strongly supported by a European Experts panel organised with the support of a pharmaceutical company [5]. Those experts recommended considering treatment using single-agent chemotherapy trials using new biological agents in PS 2 patients. They also supported the acceptance of symptomatic improvement, such as symptom relief, clinical benefit or quality of life as valid end-points in trials including only PS 2 NSCLC patients.

The use of ''low-intensity'' chemotherapy in patients with poor PS is nevertheless controversial [5]. The Cancer and Leukemia Group B (CALGB) [9] has reported improved survival in those patients when carboplatin-based chemotherapy was used compared with single-agent chemotherapy.

The European Lung Cancer Working Party has being registering in trials for advanced NSCLC

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patients with Karnofsky PS 60–70 for >25 yrs. Although poor PS was always considered a poor prognostic factor for survival, it was an independent poor prognostic factor for response in two trials [10, 11], while it was not in others [12–14]. In the present study, the recently completed randomised trial in advanced NSCLC (European Lung Cancer Working Party (ELCWP) protocol 01995) [15, 16] was retrospectively analysed in order to determine if cisplatin-based chemotherapy was associated with clinical improvement in patients with poor PS (Karnofsky 60–70).

PATIENTS AND METHODS

Selection criteria have been fully reported in the article by SCULIER *et al.* [15] dealing with the primary end-point. The principal criteria were the presence of histologically or cytologically proven, inoperable stage IV or stage IIIB (with malignant pleural effusion) NSCLC and no prior chemotherapy. Initial Karnofsky PS had to be $\geqslant$60. The protocol is fully available on the ELCWP website [17], and was approved by the ethical committee of each participating centre. The trial is an academic study according to the definition of the Belgian law based on the European directive (2001/20/CE).

Treatment consisted of three courses of gemcitabine+ifosfamide+cisplatin (GIP): gemcitabine (1 g·m^{-2} on days 1 and 8) + ifosfamide (3 g·m^{-2} on day 1) + cisplatin (50 mg·m^{-2} on day 1). Patients with a nonprogressing tumour were randomised between three further courses of GIP and three courses of paclitaxel (225 mg·m^{-2} over 3 h every 3 weeks). Patients were treated until best response. After randomisation, patients with no change or no further improvement went off treatment. Those with progressive disease were treated by paclitaxel if in the GIP group or GIP if in the paclitaxel group. Full descriptions of the treatments, work-ups, criteria of evaluation, registration and the randomisation procedure are reported elsewhere [15, 16].

The primary objective of the trial was to determine if, in patients with advanced NSCLC and nonprogressive disease after three courses of GIP, the sequential approach (GIP followed by paclitaxel) was associated with improved survival compared with the combination of GIP alone. The purpose of the present report is a retrospective analysis to determine the potential benefit of conventional cisplatin-based chemotherapy on patients with poor performance status, defined as 60–70 on the Karnofsky scale.

Survival curves were estimated by the method of Kaplan and Meier. The log rank test was used to compare survival curves. To test for differences between proportions, p-values were calculated with Chi-squared tests for homogeneity or for trend or with Fisher's exact tests. A multivariate analysis for adjustment of the treatment effect taking into account prognostic factors was performed by fitting the data with a Cox model for duration of survival and a logistic regression model for objective response. Statistical results were considered as significant when the p-value was <0.05. All reported p-values are two-tailed.

RESULTS

A total of 493 patients were registered in the trial between January 2000 and February 2004. Eight (1.6%) were ineligible for the study and 17 (3.5%) were not assessable for response. The majority (79.8%) of the eligible patients had good performance status (Karnofsky $\geqslant$80) and 20.2% had poor PS (60–70). As shown in table 1, patients with poor PS presented significantly more frequently with weight loss, anaemia and increased leukocytosis.

Of the 485 eligible patients, 410 (84.5%) received three courses of initial chemotherapy: 88.6% of the 387 patients with good PS and 68.4% of the 98 patients with poor PS (p<0.001). Of the remaining 75 (15.5%), five received no treatment (two and three with good and poor PS, respectively), 39 received one course of treatment (21 and 18 with good and poor PS, respectively), and 31 received two courses (21 and 10 with good and poor PS, respectively). Reasons for not receiving the three planned courses were as follows: early death due to tumour (n=11); cancer progression (n=15); toxic death (n=15); severe toxicity (n=13); patient intolerance (n=5); complicated tumour necrosis (n=3); and reasons leading to nonassessable disease (n=13). There was no difference in dose-intensity delivered according to initial PS (data not shown).

TABLE 1 Comparison of the baseline characteristics of the eligible patients according to their initial Karnofsky performance status (PS; good 80–100 *versus* poor 60–70)

Characteristic	PS 80–100	PS 60–70	p-value
Patients	387	98	
Sex			0.39
Male	312 (81)	83 (85)	
Female	75 (19)	15 (15)	
Age			0.74
<60 yrs	197 (51)	48 (49)	
$\geqslant$60 yrs	190 (49)	50 (51)	
Weight loss			<0.001
<5%	231 (63)	35 (42)	
$\geqslant$5%	134 (37)	49 (58)	
Missing	22	14	
Stage			0.06
III	34 (9)	3 (3)	
IV	353 (91)	95 (97)	
Type of lesions			0.25
Evaluable	99 (26)	31 (32)	
Measurable	288 (74)	67 (68)	
Histology			0.69
Squamous cell	98 (25)	26 (27)	
Adenocarcinoma	217 (56)	56 (57)	
Other	72 (19)	16 (16)	
Haemoglobin			0.008
<12 g·dL^{-1}	85 (22)	35 (36)	
$\geqslant$12 g·dL^{-1}	300 (77)	63 (64)	
Missing	2	0	
White blood cells			<0.001
$\leqslant$10000 per mm^3	240 (62)	41 (42)	
>10000 per mm^3	146 (38)	57 (58)	
Missing	1	0	

Data are presented as n or n (%).

Response to the three initial cisplatin-based chemotherapy treatments

A partial response was documented in 174 patients (36% of the eligible patients, 95% confidence interval (CI) 32–40; or 37% of the assessable patients, 95% CI 33–42) and no change in 115 (24 and 25%, respectively). Table 2 shows response distribution according to initial PS. There was a trend for a higher response rate in patients with good PS (38 *versus* 28%; p=0.06). When partial response plus no changes was considered as one group, then the response rate was significantly higher in patients with good PS (64%) than in those with poor PS (44%; p=0.001).

Univariate analysis of predictive factors for response is shown in table 3. Sex, weight loss, neutrophil and haemoglobin count proved to be significant variables. PS was not a significant variable (table 2). A multivariate analysis performed on 442 patients, using a backward procedure for selection of the covariables, identified the following criteria as independent predictive factors: sex in favour of females (odds ratio (OR) 2.22, 95% CI 1.34–3.64; p=0.002), histology in disfavour of adenocarcinoma (OR 0.47, 95% CI 0.29–0.77; p=0.002), and anaemia as measured by the haemoglobin level (OR 0.49, 95% CI 0.30–0.80; p=0.004).

Clinical improvement

PS improvement was observed in 25 out of 68 PS 2 patients evaluated as having response, no change or progression after three courses of chemotherapy. If clinical improvement in patients with poor PS is defined as obtaining a good PS during treatment (the first three courses of GIP), clinical improvement was observed in 10 (38%) out of 26 responders, three (20%) out of 15 no change patients and three (14%) out of 22 progressing patients (p=0.05). Due to missing data in five patients, the rate is calculated as 25% (16 out of 63; 95% CI 15–38%). Nine additional patients improved their Karnofsky PS from 60 to 70 during induction chemotherapy.

Responders had a quicker and higher (although statistically nonsignificant) rate of improvement than nonresponders. Among the responders, 12% had improved their PS after one course, 31% after two courses and 38% after three courses. Among the nonresponders, the rate of improvement was 3% after one course, 5% after two courses and 17% after three courses.

TABLE 2 Response distribution to the first three courses of induction gemcitabine+ifosfamide+cisplatin chemotherapy according to initial performance status (PS)

	PS 80–100	PS 60–70	p-value
Patients	387	98	
Objective response	147 (38)	27 (28)	0.06
No change	99 (26)	16 (16)	
Progression	98 (25)	25 (26)	
Tumoural necrosis	2	1	
Early death malignant	7	10	
Toxic death	8	9	
High toxicity and stop treatment	14	5	
Not evaluable	12	5	

Data are presented as n or n (%).

Survival

At the time of analysis, 440 patients had died, 35 were alive and 10 had been lost to follow-up. The median duration of follow-up was 41 months (range 0.07–66 months). Median overall survival was 8.7 months (95% CI 7.7–9.8) with 1-, 2- and 3-yr survival rates of 37% (95% CI 33–41), 15% (95% CI 11–19) and 6% (95% CI 4–8), respectively. Univariate analysis of prognostic factors for survival is summarised in table 4. The following variables were found to be statistically significant: sex, PS, weight loss, leukocytes and neutrophil counts, haemoglobin level and alkaline phosphatase. A multivariate analysis performed on 442 patients using a backward procedure for covariables selection identified female sex (hazard ratio (HR) 0.70, 95% CI 0.54–0.91; p=0.008) and Karnofsky PS $\geqslant$80 (HR 0.60, 95% CI 0.47–0.78; p $<$0.001) as independent good prognostic factors. Weight loss (HR 1.26, 95% CI 1.03–1.54; p=0.03), white blood cells (HR=1.34, 95% CI 1.09–1.65; p=0.006) and anaemia (HR 1.67, 95% CI 1.32–2.11; p$<$0.001) were identified as independent poor prognostic factors.

Toxicity

Observed toxicity during the three first courses of GIP is shown in table 5. It mainly consisted of haematological toxicity, infections and alopecia. There was no significant difference between poor and good initial PS patients for haematological toxicity but grade III alopecia was more frequent in those with good PS while diarrhoea and cardiac toxicity were more frequent in cases of initial poor PS. In total, 17 toxic deaths were observed, eight in good PS patients and nine in poor PS patients (2.1 *versus* 9.2%; p=0.002). Toxic death due to infection during neutropenia was observed in seven patients, sudden cardiac arrest in three, pulmonary embolism in two, heart failure in one, myocardial infarction in one, gastric bleeding in one, intestinal ischaemia in one and gastric perforation in one.

Further survival of responding patients according to initial PS

Survival of responders according to initial PS was calculated from the date of the fourth course or 3 weeks after the third course if no further chemotherapy was given. Of the 27 responders in the poor PS group, 23 had died at the time of analysis compared with 127 out of 147 in the good PS group. From the date of response documentation, median survival time was 49 weeks (95% CI 17–81) for the poor PS patients *versus* 51 (95% CI 41–61) for the good PS patients (p=0.47).

DISCUSSION

Combination chemotherapy was able to improve PS from Karnofsky 60–70 to 80–100 in 25% of the patients with a poor PS. Responders with initial poor PS had the highest rate of clinical improvement (39%). Of patients with no change or progressive disease, 20 and 14%, respectively, also got amelioration, achieving a good PS (Karnofsky 80–100). Responders demonstrated quicker improvement and their survival, after the three first courses of chemotherapy, was similar to that observed in responders with initial good PS. The observations of the present study suggest that patients with poor PS benefit from conventional chemotherapy.

TABLE 3 Predictive factors for response to chemotherapy: univariate analysis

Factor	Subjects	Objective response rate	OR (95% CI)	p-value
Age				
<60 yrs	245	81 (33)	1.28 (0.88–1.86)	0.22
⩾60 yrs	240	93 (39)		
Sex				
Female	90	43 (48)	1.84 (1.16–2.93)	0.01
Male	395	131 (33)		
Performance status				
⩽70	98	27 (28)	1.61 (0.99–2.63)	0.06
⩾80	387	147 (38)		
Histology				
Squamous	124	55 (44)		0.06
Adenocarcinoma	273	87 (32)	0.59 (0.38–0.91)	
Other	88	32 (36)	0.72 (0.41–1.26)	
Staging				
Stage III	37	14 (38)	0.91 (0.46–1.82)	1
Stage IV	448	160 (36)		
Type of lesions				
Evaluable	130	46 (35)	1.03 (0.68–1.57)	0.92
Measurable	355	128 (36)		
Weight loss				
<5%	266	106 (40)	0.67 (0.45–0.99)	0.05
⩾5%	183	56 (31)		
Prior surgery				
No	451	162 (36)	0.97 (0.47–2.02)	1
Yes	34	12 (35)		
White blood cell count				
⩽10000 per mm^3	281	108 (38)	0.77 (0.53–1.13)	0.21
>10000 per mm^3	203	66 (33)		
Neutrophil rate				
⩽75%	221	87 (39)	0.62 (0.40–0.98)	0.04
>75%	139	40 (29)		
Platelet count				
⩽440000 per mm^3	369	136 (37)	0.83 (0.53–1.30)	0.50
>440000 per mm^3	113	37 (33)		
Haemoglobin				
12–18 $g \cdot dL^{-1}$	361	140 (39)	0.59 (0.37–0.92)	0.02
<12 or >18 $g \cdot dL^{-1}$	122	33 (27)		
Alkaline phosphatase				
⩽110 $IU \cdot mL^{-1}$	164	56 (34)	1.15 (0.77–1.71)	0.55
>110 $IU \cdot mL^{-1}$	316	118 (37)		

Data are presented as n or n (%), unless otherwise indicated. OR: odds ratio; CI: confidence interval.

The present data confirm that PS is an extremely poor prognostic factor for survival. The four independent poor factors that were identified in the initial characteristics of the present patients were male sex, anaemia, weight loss and poor Karnofsky PS. This is in accordance with the present authors' previous trials, and with the studies specifically performed on poor PS [18, 19] but does not imply that patients do not benefit from chemotherapy. An overall survival improvement with chemotherapy *versus* supportive care alone in patients with poor PS has been shown by the Nonsmall Cell Lung Cancer Collaborative Group meta-analysis [20].

Although haematological toxicity and most of the other types of toxicity were similar between patients with poor and good PS (table 5), as it has been already shown with the carboplatin plus paclitaxel regimen [9, 19], significantly more toxic deaths (including cardiac and vascular deaths, all attributed to chemotherapy if occurring during chemotherapy) were observed in patients with poor PS (9%) in comparison with those with good PS (2%). This higher rate of toxic deaths has already been shown in the Big Lung Trial, which has similarly reported 2.8 and 7.5% risk of treatment related deaths in patients with PS 0–1 and PS 2, respectively [21].

It would be of interest to determine if this toxic death rate can be reduced with the administration of ''less intense'' regimens, without losing the associated clinical improvement. The

TABLE 4 Prognostic factors for overall survival: univariate analysis

Factor	Patients	Events	Median survival time (95% CI)	p-value
Age				0.45
<60 yrs	245	217	8.7 (7.2–10.2)	
⩾60 yrs	240	223	8.7 (7.3–10.1)	
Sex				0.006
Female	90	78	11.5 (8.05–14.5)	
Male	395	362	8.2 (7.1–9.4)	
Performance status				<0.001
⩽70	98	93	5.5 (4.0–6.9)	
⩾80	387	347	10.2 (9.0–11.3)	
Histology				0.83
Squamous	124	112	8.8 (7.3–10.3)	
Adenocarcinoma	273	247	9.3 (7.7–10.9)	
Other	88	81	8.0 (6.8–9.2)	
Stage				0.11
Stage III	37	30	12.7 (9.9–15.5)	
Stage IV	448	410	8.5 (7.4–9.6)	
Type of lesions				0.47
Evaluable	130	115	8.6 (6.7–10.5)	
Measurable	355	325	8.7 (7.5–9.9)	
Weight loss				0.002
<5%	266	239	10.8 (9.5–12.1)	
⩾5%	183	167	7.1 (6.0–8.2)	
White blood cells				<0.001
⩽10000 per mm^3	281	246	10.9 (9.8–12.0)	
>10000 per mm^3	203	193	6.6 (5.5–7.8)	
Neutrophil rate				<0.001
⩽75%	221	197	10.2 (8.5–11.8)	
>75%	139	131	6.4 (4.8–7.9)	
Platelet count				0.15
⩽440000 per mm^3	369	329	8.8 (7.5–10.1)	
>440000 per mm^3	113	108	8.3 (6.5–10.0)	
Haemoglobin				<0.001
12–18 g·dL^{-1}	361	323	10.2 (9.0–11.5)	
<12 or >18 g·dL^{-1}	122	115	6.7 (5.7–7.7)	
Alkaline phosphatase				0.02
⩽110 UI·mL^{-1}	164	145	10.9 (9.2–12.6)	
>110 UI·mL^{-1}	316	290	7.9 (7.0–8.8)	

Data are presented as n, unless otherwise stated. CI: confidence interval.

TABLE 5 Toxicity (highest grade per patient) observed for the three initial courses of chemotherapy in assessable patients according to initial performance status (PS)

Grade III–IV %	Overall	Good PS	Poor PS	p-value
Assessable patients n	474	382	92	
Leukopaenia	66	64	73	0.14
Neutropaenia	70	70	71	1
Thrombopaenia	20	19	24	0.38
Infection	7	7	9	0.50
Bleeding	<1	<1	0	1
Emesis	5.5	6	4	0.80
Diarrhoea	1	<1	3	0.05
Skin rash	<1	<1	0	1
Alopecia	23	26	13	<0.01
Mucositis	<1	<1	0	1
Peripheral neuropathy	<1	<1	2	0.17
Ototoxicity	1	0	0	
Respiratory	2	2	2	0.69
Cardiac	1.5	1	4	0.03
Renal	<1	<1	0	1

European Experts panel suggested, as a preferred option, the administration of single-agent chemotherapy with a third generation drug and, as alternative options, carboplatin-based doublets or cisplatin-based doublets with alternated doses of cisplatin [5]. The only large study to have tested one of those proposals is the CALGB analysis of study 9730 [9], which compared single-agent (paclitaxel) to combination (carboplatin plus paclitaxel) chemotherapy. Of a total of 561 randomised patients, 462 had PS 0–1 and 99 PS 2. Patients treated in the combination chemotherapy group had a statistically significantly better survival in the overall group and in the PS 2 group, but not in the PS 0–1 group. There was no difference in toxicity between both groups. Two small phase II randomised trials, specifically performed in patients with advanced NSCLC and PS 2, have been recently published. In the first trial (100 patients) conducted by the ECOG [22], platinum-based combination chemotherapy was shown to be feasible with acceptable toxicity. The regimens tested were carboplatin+paclitaxel and cisplatin+gemcitabine with a dosage of 60 mg·m^{-2} of cisplatin per cycle, in the range of the dosage used in the present study. In the second trial (90 patients) conducted by the Hellenic Cooperative Oncology Group [23], single-agent gemcitabine therapy was compared with the doublet gemcitabine+carboplatin. A trend for better response and better survival was reported in favour of the platinum-based regimen, although symptomatic improvement was similar between both groups. These data do not support the routine use of single-agent chemotherapy for the treatment of patients with poor PS. Trials performed with that approach in poor PS patients [24], without standard control group, should be interpreted with caution.

The present authors have observed clinical improvement in 25% of the patients with poor PS treated by cisplatin-based chemotherapy. It should be noted that, although significantly less frequently noted, improvement was also present in patients with no change and with progressive disease. Potential explanations for those observations are the existence of minor responses assessed as no change or of transient responses that were not documented because assessment work-up was only performed after three courses of chemotherapy. Another possibility is a biological effect of the cytotoxic therapy on the tumour, making the patient less ill by the reduction of mediators affecting patient's general condition.

The benefit of chemotherapy in poor PS patients is not a minor question. Patients with poor PS represented 20% of the patients

registered in the present trial, a prevalence similar to that reported in other studies [9, 18, 19, 21]. Responses were not observed much less frequently in those patients than in those of good PS. Objective response was documented in 28% of the poor PS patients and clinical improvement documented in 39% of the responders. In addition, as already discussed, a non-negligible rate of the other patients also had clinical improvement.

In conclusion, the present study shows that cisplatin-based chemotherapy is beneficial in patients with poor performance status, as shown by a significant improvement in performance status, with 25% of the patients reaching a good performance status. Many responders recovered a good performance status and responders with initial poor performance status had a survival similar to those with initial good performance status. A higher rate of treatment-related deaths (including cardiac and vascular fatalities) was nevertheless documented. These observations encourage the present authors to continue to include in trials and treat by conventional chemotherapy patients with advanced nonsmall cell lung cancer and poor performance status, and to systematically report subgroup analyses according to performance status. Clinical improvement should be assessed by the measure of the evolution of performance status, symptoms and quality-of-life scales.

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