

ORIGINAL ARTICLE

Chemotherapy and quality of life in NSCLC PS 2 patients

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Abstract

Introduction. Nearly 40% of patients with advanced NSCLC are in performance status (PS) 2. These patients have a shorter life expectancy than PS 0/1 patients and they are underrepresented in clinical trials. Data on how platinum-based combination chemotherapy affects Health Related Quality of Life (HRQOL) of patients with PS 2 are scarce and the treatment of this important group of patients is controversial. **Methods.** A national multicenter phase III study on platinum based chemotherapy to 432 advanced NSCLC patients included 123 patients with PS 2. To explore the treatment impact on HRQOL, the development of HRQOL during the first nine weeks were compared between PS 2 and PS 0/1 patients. We used the EORTC QLQ-C30 and QLQ-LC13 questionnaires. Standardized area under the curve for all HRQOL items, and HRQOL responses classified as better, stable or worse, were compared between the groups. **Results.** Whereas the demographic data at baseline were well balanced between the groups, the PS 2 patients had significantly worse function and more severe symptoms than the PS 0/1 patients. In response to combination chemotherapy, the PS 2 patients had a more profound improvement of global QOL, cognitive function, fatigue, dyspnea, sleeping problems and appetite loss in comparison to the PS 0/1 group. **Conclusions.** PS 2 NSCLC patients seem to achieve valuable HRQOL benefits from platinum-based combination therapy. Prospective clinical studies with predefined HRQOL outcomes in PS 2 patients are needed to confirm these findings.

Non-small cell lung cancer (NSCLC) is a common malignancy and a leading cause of cancer-death worldwide. The majority of NSCLC patients present with advanced disease [1] and palliation and health related quality of life (HRQOL) are thus important aspects of their treatment.

It is estimated that 30 – 40% of the advanced NSCLC patients present with performance status (PS) 2 [2,3]. These patients have shorter life expectancy, and their poor PS is suspected to make them more vulnerable to treatment-related side effects [4]. PS is also the strongest predictor of survival in patients with advanced NSCLC [5]. Despite these important facts, PS 2 patients have been greatly underrepresented in clinical trials.

The importance of HRQOL as an outcome of chemotherapy trials for patients with cancer is widely acknowledged. A review of 32 randomized trials examining HRQOL in patients with advanced NSCLC undergoing chemotherapy, has confirmed the superiority of chemotherapy over best supportive care regarding HRQOL and symptom improvement [6]. An Outcomes Working Group [7] within the American Society of Clinical Oncology has concluded that, even in the absence of prolonged survival, treatment guidelines can be based on improvements of HRQOL alone.

Investigations on symptomatic improvements and HRQOL benefits as trial endpoints are strongly recommended by a European Experts Panel [8].

Furthermore, the NICE guidelines on lung cancer [9] call for further research into the effects of chemotherapy on HRQOL in patients with advanced NSCLC and PS 2.

Bottomley et al. [10] reviewed HRQOL methods in 29 randomized controlled NSCLC trials. In general, they found limited details in the reporting of HRQOL results. HRQOL was mainly used as a secondary endpoint, and limited space was used for the presentation of these data. As a result, the authors suggested separate HRQOL publications in order to make adequate explanations and presentations of the findings.

Platinum-based 2-drug combination chemotherapy is the established first line treatment of advanced NSCLC [11], but remains controversial in the treatment of patients with PS 2. Several studies have concluded that combination chemotherapy should not be recommended for PS 2 patients [4,12–14]. It has been pointed out that combination chemotherapy to PS 2 patients may lead to unacceptable toxicity and that this would further compromise their already reduced HRQOL. On the other hand, combination chemotherapy was associated with improved survival when compared to single-agent therapy in advanced NSCLC PS 2 patients [15].

Limited data are available on how combination chemotherapy affects the HRQOL of PS 2 NSCLC patients. In our recent publication of treatment outcome in PS 2 advanced NSCLC patients administered platinum-based combination chemotherapy [16], a subgroup analysis of some selected HRQOL items according to performance status favored patients with PS 2. In this study we further explore the impact of combination chemotherapy on HRQOL in the PS 2 patients.

Material and methods

Patients

In our national multicenter phase III study in advanced NSCLC patients, three cycles of vinorelbine/carboplatin were compared to three cycles of gemcitabine/carboplatin with no significant differences in survival and HRQOL between the two treatment arms [17]. The study was designed to detect differences in survival and predefined HRQOL aspects between the two treatment arms. Chemonaive patients at all ages with histologically or cytologically confirmed NSCLC stage IIIB or IV, adequate bone marrow-, renal- and hepatic functions were included. PS 0–2 were allowed, using the performance status scale classified by the Eastern Cooperative Oncology Group [18]. At inclusion,

patients were stratified according to PS 0/1 vs. PS 2. In the patient population, 123 PS 2 patients were identified and their complete HRQOL data analyzed and compared to the PS 0/1 group. Survival and toxicity in the PS subgroups are published earlier [16]. Median and 1-year survival of PS 2 patients was 4.5 mths and 10% vs. 8.9 mths and 37% among PS 0/1 patients.

Chemotherapy

In both arms, three courses of chemotherapy were given at 3-week cycles. Carboplatin Chatelut AUC = 4 (equals Calvert AUC = 5), was administered day 1, and vinorelbine 25 mg/m² or gemcitabine 1 000 mg/m² day 1 and 8 in each course. Patients ≥ 75 years received 75% of standard doses. Chemotherapy was terminated in case of disease progression, unacceptable toxicity, intercurrent disease or patients' wish.

Assessment of HRQOL

We collected patient-assessed HRQOL data using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 [19] and the lung cancer specific module QLQ-LC13 [20]. The QLQ-C30 is a "core questionnaire" which incorporates a range of physical, emotional and social health issues relevant to a broad spectrum of cancer patients. Global QOL, physical-, role-, emotional-, cognitive- and social function are multi-item scales, as are fatigue, nausea/vomiting and pain. Dyspnea, insomnia, appetite loss, constipation and diarrhea are single-item measures.

The lung cancer module is validated for use in lung cancer patients. Pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia and hemoptysis are measured by single items while dyspnea is a three-item scale addressing dyspnea at rest, by walking and by climbing stairs.

The HRQOL questionnaires completed at baseline, before second and third chemotherapy cycle and three weeks after completion of chemotherapy are considered of primary interest. Time windows of ± 10 days from onset of second and third chemotherapy courses and ± 14 days for controls at week 9 were assigned.

Statistical considerations

All HRQOL items were explored, and these were scored for each patient according to the EORTC QLQ-C30 scoring manual [21]. HRQOL-item scores range from 0 to 100. A high score in functioning scales represents good function, whereas

a high score in symptom scales represents more symptoms.

The mean baseline scores for each HRQOL item were calculated and differences between the PS 0/1 and PS 2 patients were tested using the Mann-Whitney U-test.

Area under the Curve (AUC) of HRQOL scores plotted against time is a summary measure of HRQOL [22]. This provides each patient's longitudinal HRQOL experience as a single quantity and was calculated for each item [23]. To adjust for baseline differences, the AUC calculation for each patient was based on changes from baseline. Missing data were imputed. If data from one assessment point were missing, the mean value of the two adjacent ones was used. For patients who withdrew or dropped out before week 9, the last value carried forward was used to impute the missing subsequent values. This may introduce a bias if the main reason for drop-out was deterioration. To examine this possibility, comparisons were performed with data based on the worse possible score for the missing data. Standardized AUC (SAUC) was estimated as AUC divided by time. SAUC allows for differences in patient survival and corresponds to calculating the average HRQOL. SAUC from baseline to week 9 was compared between PS 0/1 and PS 2 patients using ANOVA.

Patients' responses were also classified as improved, stable or worse for all HRQOL items at week 9 according to the NCIC CTG standard QOL analysis framework [24]. Symptom or function items were considered worse if the change from baseline was >10 points towards worse without improvement at any time-point after baseline. Significant improvement was defined as ≥ 10 points towards bettering in patients who did not deteriorate. Patients, who had less than 10-point changes from baseline at every HRQOL assessment or failed to meet the criteria for worsening or improvement, were considered stable. Distributions of the categories were tested by χ^2 .

Due to multiple comparisons, p-values of <0.01 were considered significant and $p < 0.05$ indicating a tendency.

Results

Patients

Patient characteristics according to performance status are given in Table I. The PS groups were well balanced regarding baseline demographic, clinical and histological data. Of the 123 PS 2 patients, 61 were treated with vinorelbine/carboplatin and 62 with gemcitabine/carboplatin. Five did not complete

Table I. Patient characteristics at baseline.

Characteristic	PS 0/1 n = 309 (72%)		PS 2 n% n = 123 (28%)		p
	n	%	n	%	
Age, years					
Median	67		67		0.25
Range	37–86		40–84		
Age ≥ 75	62	20	25	20	0.52
Sex					
Female	120	39	48	39	0.97
Male	189	61	75	61	
Extent of disease					
St IIIB	87	28	38	31	0.57
St IV	222	72	85	69	
Histology					
Squamous cell carcinoma	79	26	31	25	0.25
Adenocarcinoma	155	50	54	44	
Large cell carcinoma	20	7	10	8	
Other	55	17	28	22	

the baseline QLQ, 4 did not receive any chemotherapy and 20 completed only the baseline QLQ. Among PS 0/1 patients the corresponding numbers were 10, 2 and 19. This leaves 372 patients for HRQOL analyses, 278 PS 0/1 patients and 94 PS 2 patients.

Chemotherapy completion

Significantly less patients in the PS 2 group received three courses of chemotherapy when compared with the PS 0/1 patients (68% vs. 85%; $p < 0.01$, Table II).

HRQOL

The compliance rate with respect to completion of the HRQOL questionnaires was 97% in both groups at baseline (Figure 1). The overall compliance during the study period was 91% and 83%, for the PS 0/1 and PS 2 group, respectively. At 3 and 6 weeks, the compliance was significantly lower in the PS 2 group (76% vs. 93% and 76% vs. 88%, $p < 0.01$). The rates of completed questionnaires within the time window of ± 10 days from onset

Table II. Completion of Chemotherapy according to Performance Status.

Courses	PS 0/1		PS 2		p
	n	%	n	%	
3	264	85	83	68	<0.01
2	26	8	12	10	0.39
1	17	6	24	20	<0.01
0	2	1	4	3	0.06

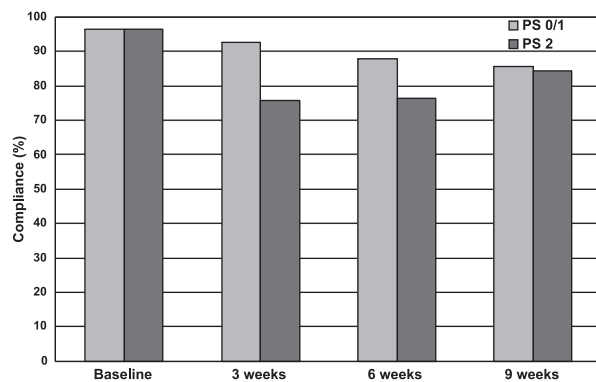


Figure 1. Compliance of Quality of Life Questionnaires during the period of interest.

of second and third chemotherapy courses were 95% and 94%, and 89% within ± 14 days of follow-up at week 9 without significant differences between the two subgroups.

The two PS subpopulations differed significantly at baseline (Figure 2). The PS 2 patients reported lower function for all the functional scales ($p < 0.01$). They also had significantly more severe symptoms with more fatigue, pain, dyspnea, swallowing problems, cough, nausea, insomnia, appetite loss and constipation (symptom scales, $p < 0.01$).

The SAUC based on imputation by carrying the last value forward, is presented in Table III. Results

from imputation of worst possible scores were consistent with the presented data. Regarding the function scales, a tendency towards improved global QOL was achieved among PS 2 patients. For symptoms, they achieved significantly relief of fatigue, dyspnea and sleeping problems, and they tended towards less pain and appetite loss. In no items did PS 2 patients experience significant deterioration when compared to PS 0/1 patients.

The proportions of patients classified as improved, stable or worse are presented in Table IV. PS 2 patients achieved improvement in global QOL and cognitive function and tended towards improvement of role function. They also experienced relief of dyspnea measured by QLQ-C30, and tended to improvement of fatigue, swallowing problems and appetite.

Discussion

In the present study of combination chemotherapy, PS2 patients had more improvement of global QOL, cognitive function, fatigue, pain, dyspnea, sleeping problems and appetite loss than PS 0/1 patients.

The differences in HRQOL gains are not surprising. Taking into account the heavier baseline symptom burden of PS 2 patients, they clearly have the greatest potential for palliation and HRQOL improvements.

The HRQOL benefits seen among our PS 2 patients are consistent with previous studies. Billingham and Cullen found superior palliation among PS 2 patients in comparison to PS 0/1 [12] in two randomized trials using mitomycin, ifosfamide and cisplatin in the treatment of unresectable NSCLC [25]. Furthermore, in a recent randomized phase II study on first line erlotinib versus standard chemotherapy of PS 2 advanced NSCLC patients, HRQOL tended to improve rather than worsen in both treatment arms [26]. In fact, the authors concluded that unselected advanced NSCLC PS 2 patients are best treated with combination chemotherapy in first-line.

A major strength of this prospective study is HRQOL analyses based on an unselected lung cancer population, largely reflecting the everyday clinical setting. The high average age and the large proportion of PS 2 patients reflects the high grade of representativity, as nearly 40% of diagnosed advanced NSCLC patients nationally during the accrual period were included in this study.

Missing data in trials involving HRQOL represents, on the other hand, a well known and described challenge [27]. Deteriorating patients are likely to have an increased drop-out rate in completing HRQOL questionnaires [28], and the lower

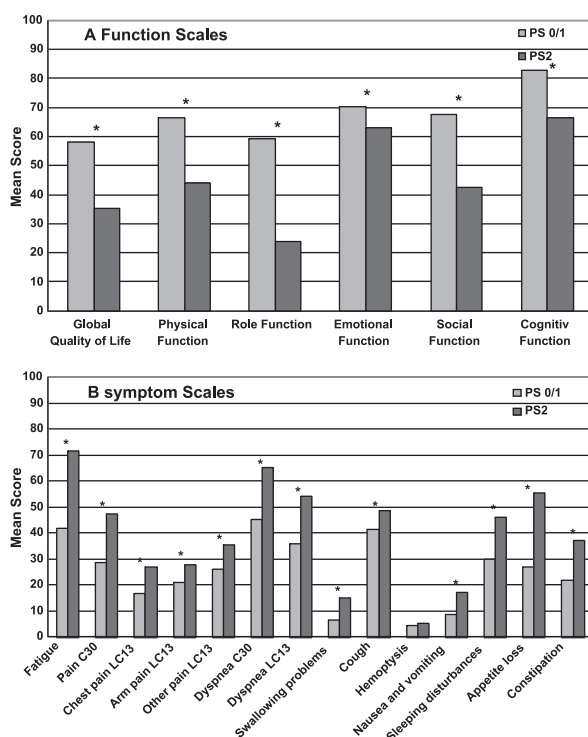


Figure 2. Mean HRQOL scores at baseline. Panel A: Functioning scales. A high function score represents good function. Panel B: Symptom scales. A high symptom score represents more symptoms. * $p < 0.01$.

Table III. Standardized Area under Curve According to Performance Status for the HRQOL items.

Outcome	PS 0/1		PS 2		p
	n	SAUC*	n	SAUC*	
Function					
Global QOL	276	−1.9	93	2.5	0.05
Physical function	278	−5.6	94	−4.4	0.46
Role function	278	−8.0	94	−3.5	0.12
Emotional function	277	3.1	94	2.7	0.81
Social function	277	−5.5	94	−3.9	0.52
Cognitive function	277	−1.8	94	0.1	0.29
Symptoms					
Fatigue	278	5.6	94	−1.3	<0.01
Pain C30	278	−1.5	94	−6.7	0.03
Chest pain LC13	275	2.0	94	−3.1	0.02
Arm/shoulder pain LC13	277	1.2	94	−4.3	0.03
Pain elsewhere LC13	274	1.5	91	0.4	0.70
Dyspnea C30	278	0.6	93	−6.7	<0.01
Dyspnea LC13	276	2.2	94	−0.8	0.16
Swallowing problems	277	1.3	94	−0.1	0.51
Cough	277	−7.3	94	−9.1	0.50
Hemoptysis	278	−0.4	94	−1.4	0.42
Nausea/vomiting	278	4.2	94	3.2	0.60
Insomnia	278	−1.5	94	−9.7	<0.01
Sore mouth	277	5.5	93	5.3	0.94
Neuropathy	275	3.2	94	5.8	0.22
Hair loss	276	6.5	94	6.8	0.89
Appetite loss	278	3.9	94	−2.9	0.03
Constipation	273	13.0	94	9.9	0.32
Diarrhea	278	−1.6	94	−1.0	0.77

*SAUC is Area under Curve pr week during the period of interest. A positive SAUC indicates improved function or more symptoms. Oppositely, a negative SAUC represents worsened function or improvement in symptoms.

compliance among PS 2 patients at weeks 3 and 6 may be a weakness. Another important issue is the chance of type I error as false positives may result from multiple testing in post hoc analyses [29]. Although a significance level defined at $p < 0.01$ to a certain degree can compensate for this [30], the results of our HRQOL analyses should be interpreted with caution. Nevertheless, new HRQOL data on PS 2 patients treated with combination chemotherapy are essential and provide valuable information.

Dyspnea, pain and fatigue are described as the most distressing symptoms in advanced NSCLC [31] and consequently these symptoms are of substantial clinical interest. In our population, these symptoms were at baseline significantly worse, but actually palliated to a larger extent in PS 2 patients when compared to PS 0/1. Surprisingly, PS 2 patients did not seem to deteriorate in any of the HRQOL dimensions when compared to the PS 0/1 patients.

Concerns have been raised that chemotherapy to PS2 patients may further deteriorate already compromised HRQOL aspects. Current guidelines have cautioned against the use of combination chemotherapy in these patients [11]. The results of

the present study challenge these conservative therapeutic attitudes towards PS 2 patients. We found clinically relevant palliation of traumatic symptoms like fatigue, pain, dyspnea, appetite loss, sleeping problems and improved global QOL, role function and cognitive function in these patients.

In conclusion, combination chemotherapy to motivated PS 2 NSCLC patients should not be controversial from a HRQOL perspective. There are no convincing data indicating that such treatment deteriorates HRQOL in this patient population. On the contrary, clinically meaningful improvements of symptoms and function can be achieved. Further prospective studies with predefined HRQOL outcomes in PS 2 patients are warranted to confirm these findings.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Table IV. Health related Quality of Life Responses according to Performance Status

	PS 0/1				PS 2				p
	%				%				
	n	Improved	Stable	Worse	n	Improved	Stable	Worse	
Function									
Global QOL	276	32	24	44	93	48	13	39	<0,01
Physical function	278	20	26	54	94	27	20	53	0,26
Role function	278	26	15	59	94	38	20	42	0,01
Emotional function	277	35	40	25	94	37	32	31	0,29
Social function	277	31	19	50	94	34	17	49	0,80
Cognitive function	277	26	33	41	94	39	18	43	<0,01
Symptoms									
Fatigue	278	32	11	57	94	48	8	44	0,03
Pain C30	278	36	29	35	94	48	20	32	0,09
Chest pain LC13	275	20	45	35	94	32	42	26	0,06
Arm/shoulder pain LC13	277	21	50	29	94	30	39	31	0,12
Pain elsewhere LC13	274	26	39	35	91	32	34	34	0,50
Dyspnea C30	278	29	35	36	93	54	20	26	<0,01
Dyspnea LC13	276	32	17	51	94	44	13	43	0,10
Swallowing problems	277	10	68	22	94	17	54	29	0,04
Cough	277	45	37	18	94	45	30	25	0,26
Hemoptysis	278	8	81	11	94	10	80	10	0,76
Nausea/vomiting	278	19	38	43	94	29	30	41	0,13
Insomnia	278	34	37	29	94	43	39	19	0,11
Sore mouth	277	9	57	34	93	9	60	31	0,87
Neuropathy	275	13	57	30	94	9	52	39	0,20
Hair loss	276	6	59	35	94	6	57	37	0,93
Appetite loss	278	26	36	38	94	40	26	34	0,02
Constipation	273	15	29	56	94	22	29	49	0,23
Diarrhea	278	25	53	22	94	20	56	24	0,66

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