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Influence of comorbidity on survival, toxicity and health-related quality of life in patients with advanced non-small-cell lung cancer receiving platinum-doublet chemotherapy

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ABSTRACT

Aim of the study: To investigate whether patients with severe comorbidity receiving platinum-based chemotherapy for advanced non-small-cell lung cancer (NSCLC) have a shorter overall survival, experience more toxicity or more deterioration of health-related quality of life (HRQoL) than other patients during treatment.

Patients and methods: Patients enrolled onto a phase III trial comparing pemetrexed/carboplatin with gemcitabine/carboplatin as first-line therapy of stage IIIB/IV NSCLC were analysed. Eligible patients had performance status 0–2 and adequate kidney/liver/bone-marrow function. Comorbidity was assessed from hospital medical records using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G). Toxicity was graded using the CTCAE v3.0 and the patients reported HRQoL on the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30/LC13.

Results: Data from 402 of the 436 of the patients enrolled onto the phase III trial were analysed. The patients with severe comorbidity had similar survival as other patients (6.9 versus 8.1 months; $p = .34$), similar frequency of neutropenia (48% versus 42%; $p = .16$), but experienced more neutropenic fevers (12% versus 5%; $p = .012$) and deaths from neutropenic infections (3% versus 0%; $p = .027$). They had more thrombocytopenia (46% versus 36%; $p = .03$), but not more thrombocytopenic bleedings (3% versus 4%; $p = .65$). In general, the patients with severe comorbidity reported poorer HRQoL, but not significantly more deterioration of HRQoL.

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Conclusions: The results from our study suggest that patients with advanced NSCLC who have severe co-existing disorders benefit from and tolerate platinum-doublet chemotherapy as well as other patients. They do, however, appear to have a higher risk of acquiring infections when neutropenic.

1. Introduction

Lung cancer is one of the most common malignant diseases and the leading cause of cancer-deaths worldwide. Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of the cases and about half of the patients are diagnosed with advanced disease. Platinum-based chemotherapy is the recommended palliative therapy for these patients as it prolongs survival and improves health-related quality of life (HRQoL).[1,2] Such treatment is, however, often withheld from patients with significant comorbidity – especially elderly.[3] One reason may be concerns about negative side-effects in terms of toxicity and deterioration of HRQoL,[2,4] although the documentation for this is scarce: in clinical trials, comorbidity is seldom systematically assessed and reported, and elderly and patients with significant comorbidity are often underrepresented.[5,6]

Comorbidity increases with age,[7] and due to a growing population of elderly cancer patients, there is a need to define how patients with co-existing disorders should be treated. This is particularly true for lung cancer patients; the median age is approximately 70 years,[8] and as a majority have been tobacco-smokers – a well-known risk factor for a wide range of diseases – co-existing diseases are frequent.[7,9,10]

Comorbidity has been identified as an independent prognostic factor for survival in several cancers.[11,12] The results from studies of NSCLC are, however, not consistent. Whereas a negative association between the presence of comorbidity and survival has been demonstrated in studies of stage I[9] and stage III[10] and cohorts of mixed stages,[13,14] this has not been confirmed in advanced disease.[12,15,16] Only a few have studied whether NSCLC-patients with severe comorbidity experience more treatment related toxicity than other patients,[13,17] and no studies have investigated the impact on HRQoL during chemotherapy in this population.

The Norwegian Lung Cancer Study Group conducted a phase III trial comparing pemetrexed plus carboplatin with gemcitabine plus carboplatin as first-line chemotherapy of advanced NSCLC.[18] The aim of the present, exploratory subset analyses was to investigate whether the patients with severe comorbidity enrolled onto the study had a shorter median overall survival, experienced more toxicity or more deterioration of HRQoL during the study treatment than the patients with a better general health.

2. Patients and methods

2.1. Approvals

The study was approved by the Regional Committee for Medical Research Ethics in Central Norway, the Norwegian Medicines Agency, the Norwegian Social Science Data Services and the Norwegian Directorate for Health and Social Affairs.

2.2. Methods and results from the main study

The methods and results of the randomised phase III trial, upon which the present subset analyses are based, have been reported previously.[18] The study was designed to compare two platinum-doublet chemotherapy regimens as first-line therapy of advanced NSCLC. The primary end-point was HRQoL (global quality of life, fatigue, nausea/vomiting and dyspnoea), secondary end-points were overall survival and toxicity. From May 2005 until July 2006, 436 eligible patients were enrolled at 35 hospitals in Norway. No significant differences in HRQoL or survival were found between the treatment arms. There was more haematologic toxicity on the gemcitabine-arm, but not more of other grade 3–4 adverse events. Thus, for the present study, data from both treatment arms have been analysed jointly.

Eligible patients had given written informed consent, had stage IIIB (ineligible for curative radiotherapy) or stage IV NSCLC, WHO performance status 0–2, platelets $\geqslant 100 \times 10^9$/L, absolute neutrophil count $\geqslant 1.5 \times 10^9$/L, creatinine-clearance $\geqslant 45$ ml/min (Cockcroft-Gault), bilirubin $<1.5 \times$ ULN, ALT and ALP $<3 \times$ ULN. All other comorbidities were allowed.

With a 3-week interval, up to four cycles of carboplatin AUC = 5 (Calvert) on day 1 plus either pemetrexed 500 mg/m^2 on day 1 or gemcitabine 1000 mg/m^2 on days 1 and 8 were administered. Those who were $\geqslant 75$ years had a 25% dose reduction based on the study-group's experience from a previous trial (unpublished data).

Patients underwent laboratory tests and completed HRQoL-questionnaires before each chemotherapy-cycle (weeks 0, 3, 6 and 9) and at follow-up visits every 8 weeks from weeks 12 to 52. Toxicity was graded using the CTCAE v3.0.

HRQoL was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 and the lung cancer specific module LC13. The QLQ-C30 measures fundamental aspects of HRQoL and symptoms commonly reported by cancer patients in general, the LC13 measures symptoms commonly associated with lung cancer and its treatment.

Global quality of life (QoL), fatigue, nausea/vomiting (reported on the C30) and dyspnoea (reported on the LC13) were defined as the primary HRQoL-end-points. Global QoL gives information on overall health. Nausea/vomiting and fatigue are common, important side-effects of chemotherapy. Fatigue and dyspnoea are key symptoms of lung cancer.

2.3. Assessment of comorbidity

The Cumulative Illness Rating Scale for Geriatrics (CIRS-G) is an index of fourteen scales/organ systems.[19,20] The severity of disorders on each scale is graded from 0 to 4. '0' indicates no problem, '1' a current mild problem or past significant

problem, '2' a moderate disability or morbidity requiring 'first-line' therapy, '3' a severe/constant significant disability or an 'uncontrollable' chronic problem and '4' an extremely severe/immediate treatment required/end organ failure/severe impairment in function. A manual recommends specific scores for common conditions.[20] The total score (=sum of scores on all scales), the numbers of scores 3 and 4 and the severity index (=total score/number of categories with a score >0) are then calculated (Table 1).

Two physicians independently assessed comorbidity for each patient from hospital-charts for the last three months prior to randomisation. Any differences in scores were discussed and the two physicians agreed on a final score. The most common cause of inconsistent scores was that information in the charts had been overlooked. Three of the authors, all physicians and specialists in oncology, did the assessment.

2.4. *Analyses and statistical considerations*

In two studies of NSCLC, patients with a severity index >2 or ⩾1 CIRS-G score 4 had inferior survival.[9,10] Thus, we defined 'high severity index' as >2 and 'extremely severe comorbidity' as the presence of ⩾1 CIRS-G score 4. Since it may be difficult to differentiate whether a disorder qualifies for a score 3 or 4,[21] we additionally defined 'severe comorbidity' as the presence of ⩾1 CIRS-G score 3 or 4.

Survival time was defined as time from randomisation until death and was estimated using the Kaplan–Meier method. The log-rank test was used in the univariate survival-analyses to compare survival according to comorbidity-scores and other known prognostic factors in advanced NSCLC; performance status (PS),[22] stage of disease,[23] gender,[24] smoking-history[25] and baseline HRQoL[14,15,26] – as well as study treatment. Based on the results from previous studies,[15,26] appetite loss (baseline score >0) and global quality of life (QoL) (cut-off level at 66) were defined as the most important prognostic baseline HRQoL-scores. Cox multivariate-analyses were conducted adjusting for the baseline characteristics identified as significant prognostic factors in the univariate survival-analyses. Toxicity data were compared using Pearson's Chi-Square and Fischer's exact tests.

HRQoL-scores were calculated according to the EORTC QLQ-C30 scoring manual. The mean scores and areas under the curves (AUC) for the first 20 weeks were then compared. Mean scores were calculated from the reported values only. Missing data were imputed before calculating AUCs. Missing intermittent scores were replaced by the mean value of the two adjacent scores. Last reported value was carried forward for other missing values unless the patient died. In those cases, the missing values were set to zero from the time of death. A sensitivity test was performed using the same method for imputing missing intermittent values, but with the last value carried forward, even after death. The AUCs for each scale were compared using linear regression adjusting for the baseline HRQoL-scores.

The clinically relevant minimum difference in mean HRQoL-scores was defined as 10 points (on a scale from 0 to 100).[27] Statistical significance level was defined as $p < 0.05$.

Table 1 – Example of comorbidity assessment in a patient using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G).

Score	0	1	2	3	4
Heart		X			
Vascular			X		
Haematopoietic	X				
Respiratory				X	
Eyes, ears, nose, throat and larynx	X				
Upper gastrointestinal tractus	X				
Lower gastrointestinal tractus		X			
Liver	X				
Renal	X				
Genitourinary		X			
Musculoskeletal/integument	X				
Neurological	X				
Endocrine/metabolic and breast	X				
Psychiatric illness	X				
Total number of categories endorsed				5	
Total score				8	
Severity index (total score/total number of categories endorsed)				1.6 (8/5)	
Number of categories at level 3				1	
Number of categories at level 4				0	

Rating strategy
0 – no problem
1 – current mild problem or past significant problem
2 – moderate disability or morbidity/requires 'first-line' therapy
3 – severe/constant significant disability/'uncontrollable' chronic problems
4 – extremely severe/immediate treatment required/end organ failure/severe impairment in function

3. Results

3.1. *Patients*

Patients who completed the baseline QLQ, received at least one cycle of chemotherapy and had copies of their hospital medical records sent to the study office (402 of the 436 patients enrolled onto the phase III trial) were analysed in the present study (Fig. 1). Age distribution and the proportion of new cases of NSCLC in Norway accrued in each age group are shown in Fig. 2A; 23% of patients <70 years and 12% of patients ⩾70 years were enrolled ($p < .001$).

Baseline characteristics for all patients and for subgroups defined according to CIRS-G scores are shown in Table 2. Median age of all patients was 65 years, 36% were ⩾70 years, 18% were ⩾75 years, 58% men, 79% had PS 0–1 and 29% had stage IIIB. The baseline characteristics were well balanced between the patients with high and low severity index. There were more elderly, males and stage IIIB among the patients with severe comorbidity than among those with less comorbidity.

3.2. *Comorbidity*

The distributions of the total CIRS-scores and the severity indices are shown in Fig. 2B and C. The median total CIRS-G score

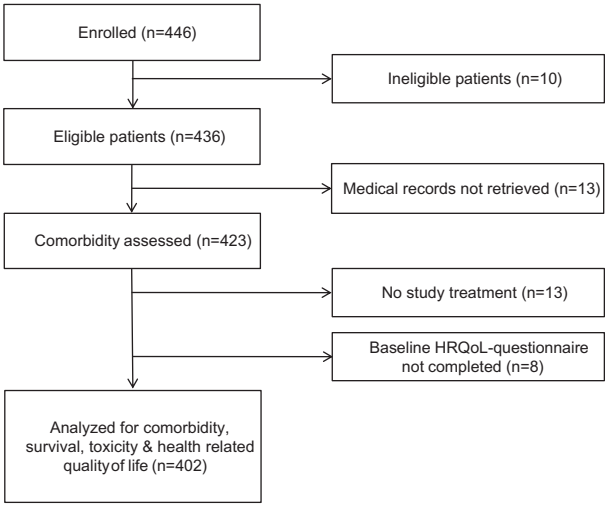

Fig. 1 – Patient selection.

was 7 (range 0–17). Only three patients had no comorbidity, 8% had no CIRS-G scores >1, 49% had severe comorbidity (⩾ one CIRS-G score 3–4), 9% had extremely severe comorbidity (⩾ one CIRS-G score 4) and 15% had a high severity index (>2).

Most CIRS-G scores 3 and 4 were registered on the respiratory (25%), vascular (10%) and heart (10%) scales (Fig. 2D); 68% of the patients with severe comorbidity had disorders on these scales only.

3.3. *Study treatment*

When comparing patients with and without severe comorbidity, there were no significant differences in the mean number of chemotherapy-cycles administered (3.2 versus 3.5; $p = .05$) or the proportion of patients who completed all four cycles (65% versus 73%; $p = .08$). Fewer patients with severe comorbidity completed four cycles without delays (46% versus 59%; $p = .008$), but those who completed all cycles did not have more dose reductions (29% versus 35%; $p = .17$) (Table 2). Fewer of the patients with severe comorbidity received second-line systemic therapy (27% versus 26%; $p = .04$) or post-study radiotherapy (35% versus 48%; $p = .01$).

There were no differences in study-treatment or post-study therapy depending on the presence of extremely severe comorbidity or a high severity index.

3.4. *Survival*

There were no significant differences in survival when comparing patients with and without severe comorbidity (6.9 versus 8.1 months; $p = .34$), with and without extremely severe comorbidity (6.7 versus 7.7 months; $p = .88$) and patients with a high severity index versus those with a low (8.4 versus 7.4 months; $p = .76$) (Fig. 3). Nor did the patients with severe comorbidity have significantly different survival compared with the other patients within any of the treatment arms (PC: 6.7 versus 9.4 months; $p = .18$, GC: 7.2 versus 7.3 months;

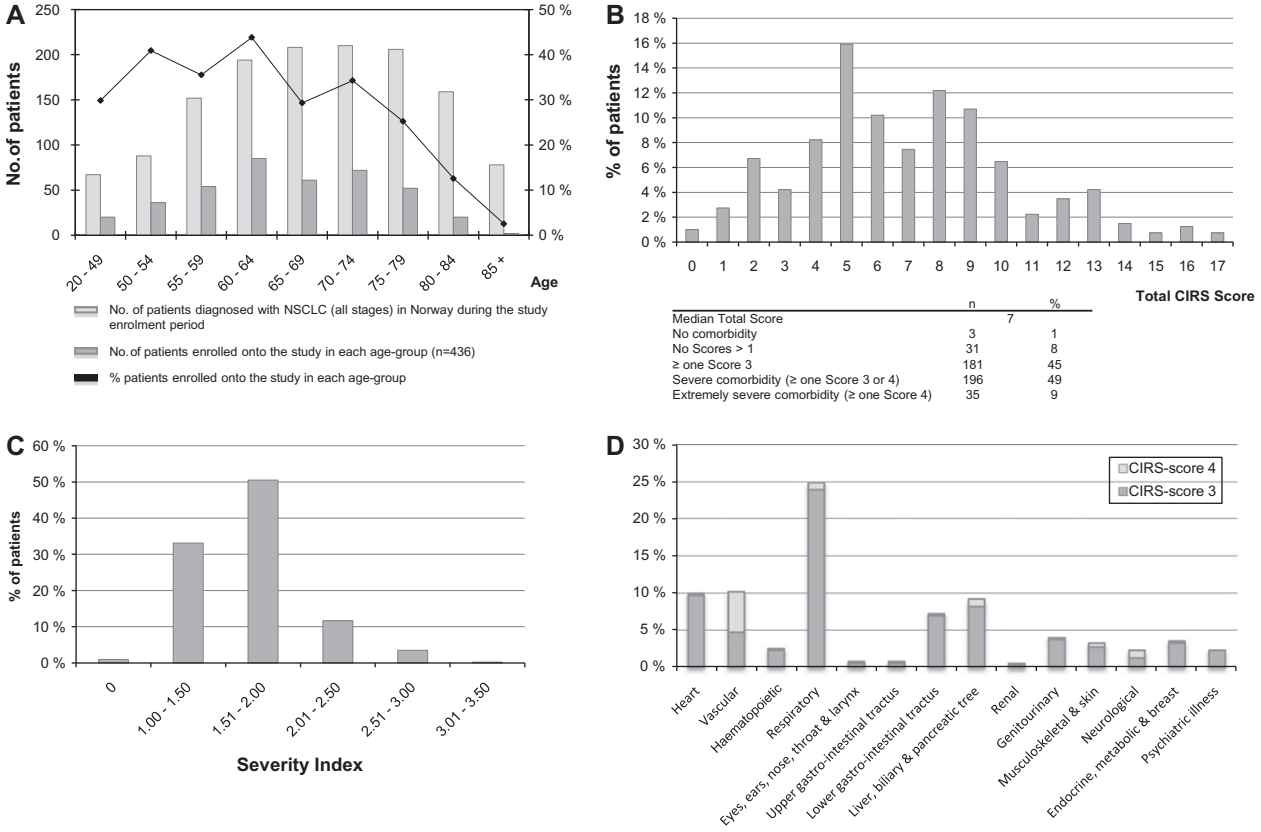

Fig. 2 – Age distribution of patients and inclusion-rate in each age group (A) distribution of total CIRS-scores (B) severity indices (C) and the prevalence of grade 3–4 comorbidity on the different cumulative illness rating scale for geriatrics (CIRS-G) scales (D).

Table 2 – Baseline patient characteristics, study treatment and post-study therapy for all patients and grouped depending on the presence of severe comorbidity (⩾ one CIRS-G score 3–4) or a high severity index (>2).

Characteristic	All patients (n = 402)		No severe comorbidity (n = 206)		Severe comorbidity (n = 196)			Low severity index (n = 340)		High severity index (n = 62)		
	No. of Pts.	%	No. of Pts.	%	No. of Pts.	%	p	No. of Pts.	%	No. of Pts.	%	p
Age, years												
Median	65		63		67			65		66		
Range	(25–90)		(25–90)		(41–84)			(25–90)		(50–84)		
⩾75 years	74	18	30	15	44	22	.04	62	18	12	19	.83
Gender												
Male	231	57	105	51	126	64		192	56	39	63	
Female	171	43	101	49	70	36	.007	148	44	23	37	.35
Performance status												
0–1	318	79	165	80	153	78		270	79	48	77	
2	84	21	41	20	43	22	.62	70	21	14	23	.72
Extent of disease												
Stage IIIB	116	29	48	23	68	35		96	28	20	32	
Stage IV	286	71	158	77	128	65	.01	244	72	42	68	.52
Histology												
Squamous cell carcinoma	99	25	40	19	59	30		80	24	19	31	
Adenocarcinoma	202	50	108	52	94	48		167	49	35	56	
Large cell carcinoma	24	6	11	5	13	7		23	7	1	2	
Other	77	19	47	23	30	15	. 08	70	21	7	11	.16
Smoking history												
Never-smoker	29	7	20	10	9	5		26	8	3	5	
Former smoker	210	52	114	55	96	49		178	52	32	52	
Current smoker	159	40	70	34	89	45		133	39	26	42	
Unknown	4	1	2	1	2	1	.05	3	1	1	2	.81
Treatment												
Study treatment												
Pemetrexed/carboplatin	197	49	107	52	90	46		168	49	29	47	
Gemcitabine/carboplatin	205	51	99	48	106	54	.23	172	51	33	53	.70
Completed four cycles	279	69	151	73	128	65	.08	239	70	40	65	.36
Four cycles without delay	212	53	122	59	90	46	.008	179	53	33	53	.93
Four cycles without dose reduction	128	32	72	35	56	29	.17	106	31	22	35	.50
Mean no. of cycles	3.3		3.5		3.2		.05	3.4		3.3		.44
Second-line systemic therapy	126	31	74	36	52	27	.04	106	31	20	32	.87
Second-line chemotherapy	94	23	56	27	38	19	.07	79	23	15	24	.87
Second-line EGFR-TKI	32	8	18	9	14	7	.56	27	8	5	8	.97
Post-study palliative radiotherapy	167	42	98	48	69	35	.01	147	43	20	32	.11

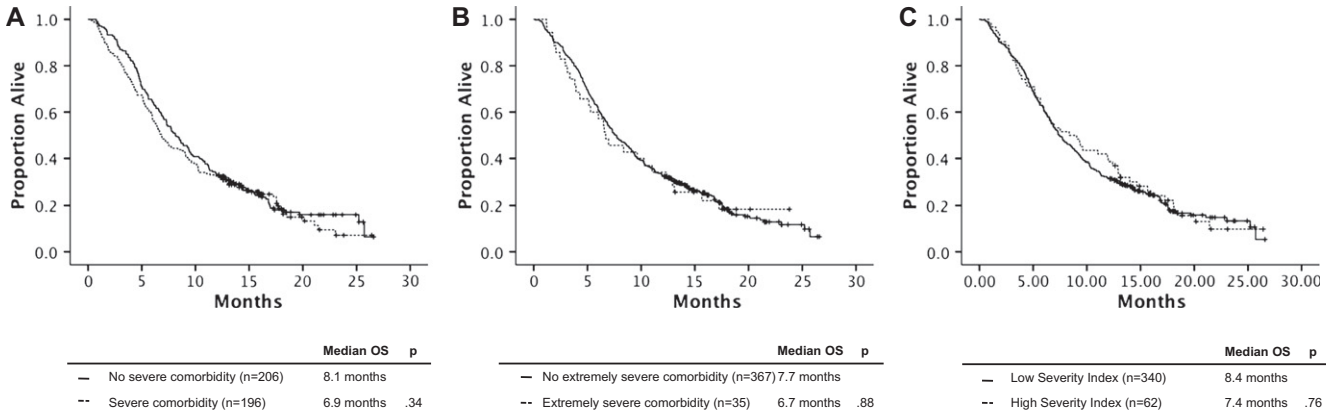

Fig. 3 – Survival curves for patients with and without severe comorbidity (⩾ one CIRS-G score 3 or 4) (A), with and without extremely severe comorbidity (⩾ one CIRS-G score 4) (B) and a low or a high severity index (>2) (C).

Table 3 – Survival-analyses. The multivariate-analyses were performed adjusting for all significant prognostic factors in the univariate analyses. A high global QoL was defined as ⩾66, severe comorbidity as the presence of ⩾one CIRS-G score 3 or 4, extremely severe comorbidity as ⩾ one CIRS-G score 4 and a high severity index as >2.

		Estimate (months)	95% confidence interval (CI)		Estimate (months)	95% CI	Log-rank *p*-value
Univariate analyses							
Performance status	0–1 (*n* = 318)	8.5	7.4–9.6	2 (*n* = 84)	5.1	3.8–6.5	.001
Stage	IIIB (*n* = 116)	8.8	6.8–10.7	IV (*n* = 286)	7.3	6.4–8.3	.15
Gender	Women (*n* = 171)	9.1	7.5–10.6	Men (*n* = 231)	6.6	5.9–7.3	.02
Smoking history	Never-smoker (*n* = 21)	11.9	9.3–14.4	Ever-smoker (*n* = 369)	7.3	6.5–8.1	.07
Age	<75 years (*n* = 328)	7.7	6.6–8.8	⩾75 years (*n* = 74)	7.3	4.7–10.0	.89
Study treatment	Pemetrexed/ carboplatin (*n* = 197)	7.9	6.5–9.4	Gemcitabine/ carboplatin (*n* = 205)	7.3	6.1–8.5	.46
Baseline HRQoL	High global QoL (*n* = 146)	9.3	7.7–10.9	Low global QoL (*n* = 256)	6.7	5.9–7.6	.004
	No appetite loss (*n* = 186)	9.3	7.7–10.9	Appetite loss (*n* = 216)	6.5	5.7–7.4	.006
Comorbidity	No severe comorbidity (*n* = 206)	8.1	6.9–9.3	Severe comorbidity (*n* = 196)	6.9	5.9–7.8	.34
	No extremely severe comorbidity (*n* = 367)	7.7	6.7–8.7	Extremely severe comorbidity (*n* = 35)	6.7	4.0–9.4	.88
	Low severity index (*n* = 340)	7.4	6.5–8.4	High severity index (*n* = 62)	8.4	5.3–11.4	.76
					HR	95% CI	*p*-value
Mutltivariate analyses							
Performance status	0–1 (*n* = 318)		v	2 (*n* = 84)	.74	.56–.96	.03
Stage	IIIB (*n* = 116)		v	IV (*n* = 286)	.80	.62–1.03	.08
Gender	Women (*n* = 171)		v	Men (*n* = 231)	.76	.61–.96	.02
Smoking history	Never-smoker (*n* = 21)		v	Ever-smoker (*n* = 369)	.66	.42–1.024	.06
Age	<75 years (*n* = 328)		v	⩾75 years (*n* = 74)	.97	.73–1.29	.83
Treatment	Pemetrexed/ carboplatin (*n* = 197)		v	Gemcitabine/ carboplatin (*n* = 205)	.98	.78–1.22	.85
Baseline HRQoL	High global QoL (*n* = 146)		v	Low global QoL (*n* = 256)	.78	.61–1.004	.05
	No appetite loss (*n* = 186)		v	Appetite loss (*n* = 216)	.79	.63–1.00	.05
Comorbidity	No severe comorbidity (*n* = 206)		v	Severe comorbidity (*n* = 196)	.95	.76–1.19	.66
	No extremely severe comorbidity (*n* = 367)		v	Extremely severe comorbidity (*n* = 35)	.98	.66–1.44	.90
	Low severity index <2 (*n* = 340)		v	High severity index (*n* = 62)	1.09	.81–1.48	.56

p = .97), within the subgroup of patients with PS 2 (5.1 versus 5.9 months; p = .69) or among patients ⩾75 years (6.3 versus 7.8 months; p = .69).

PS (p = .001), gender (p = .02), baseline global QoL (p = .004) and appetite loss (p = .006) were significant prognostic factors in the univariate survival-analyses. According to the multivariate survival-analyses, PS (0–1 versus 2: HR .74; 95% confidence interval (CI) .56–.96) and gender (women versus men: HR .76; 95% CI .61–.96) but none of the comorbidity-scores were significant prognostic factors (Table 3).

3.5. Toxicity

The patients with severe comorbidity developed significantly more often grade 3–4 thrombocytopenia than those with less comorbidity (46% versus 36%; p = .03), but did not experience more thrombocytopenic bleedings (3% versus 4%; p = .65). The frequency of grade 3–4 neutropenia was comparable (48% versus 42%; p = .16), whereas significantly more neutropenic fevers (12% versus 5%, p = .01) and all deaths from neutropenic infections (3% versus 0%, p = .03) were observed among the patients with severe comorbidity (Table 4). These patients also had more deaths from other adverse events during the treatment period (3% versus 7%; p = .05). When looking at the subgroup of patients <75 years, the same pattern of differences in toxicity depending on the presence of severe comorbidity was observed.

The patients with severe comorbidity who developed neutropenic fevers had disorders on the following CIRS-G scales: heart (n = 8), vascular (n = 7), respiratory (n = 11), genitourinary (n = 1) and psychiatric (n = 1). The patients who died from neutropenic infections had severe comorbidity in the respiratory (n = 4) and the vascular system (n = 1).

Extremely severe comorbidity or a high severity index did not predict more grade 3–4 adverse events.

3.6. Health-related quality of life

Compliance of the HRQoL-questionnaires during the first 20 weeks was 88%, and was similar in all subgroups. At all time points for assessment of HRQoL, the mean scores indicated that patients with severe comorbidity had a poorer HRQoL when compared to the other patients (Fig. 4). However, the difference only exceeded 10 points at one time point (week 12) and only on three of four scales (global QoL, fatigue and dyspnoea).

When comparing AUCs, the patients with severe comorbidity had significantly worse global QoL (p = .01), more fatigue (p = .001) and dyspnoea (p = .01), whereas nausea/vomiting was comparable to what the patients with less comorbidity reported (p = .31). The sensitivity tests confirmed the difference for global QoL (p = .002), but not for fatigue (p = .48), nausea/vomiting (p = .86) or dyspnoea (p = .28).

On the other HRQoL-scales, there was a trend towards worse physical and role functioning among the patients with severe comorbidity. Extremely severe comorbidity or a high severity index did not predict significant differences in HRQoL during the study treatment.

4. Discussion

None of the comorbidity-scores were significant prognostic factors for survival in our study population. This contrasts the results from previous studies of patients with localised disease and mixed cohorts of NSCLC-patients,[9,10,12–14] but are consistent with studies of patients with metastatic disease[12],

Table 4 – Adverse events depending on comorbidity (occurring in more than 1% of the patients).

Adverse events	No severe comorbidity (n = 206)		Severe comorbidity (n = 196)			Low severity index (n = 340)		High severity index (n = 62)		
	No. of Pts.	%	No. of Pts.	%	p	No. of Pts.	%	No. of Pts.	%	p
Grade 3–4 haematologic toxicity										
Anaemia	26	13	26	13	.85	47	14	5	8	.21
Leukopenia	67	33	68	35	.65	113	33	22	35	.73
Neutropenia	86	42	94	48	.16	150	45	30	48	.57
Thrombocytopenia	74	36	92	46	.03	137	40	29	47	.34
Grade 3–4 non-haematologic adverse events										
Infection without neutropenia	14	7	20	10	.22	28	8	6	10	.71
Neutropenic fever	10	5	23	12	.01	26	8	7	11	.34
Nausea	10	5	5	3	.22	13	4	2	3	1.0
Thrombocytopenic bleeding	8	4	6	3	.65	13	4	1	2	.71
Other	12	6	16	8	.36	25	7	3	5	.60
One or more adverse event	45	22	49	25	.46	81	24	13	21	.63
Death from adverse events										
Neutropenic infection	0	0	5	3	.03	3	1	2	3	.17
Infection	4	2	4	2	1.0	8	2	0	0	.62
Other	2	1	5	3	.11	4	1	2	3	.23
Total	6	3	14	7	.05	15	4	4	6	.51

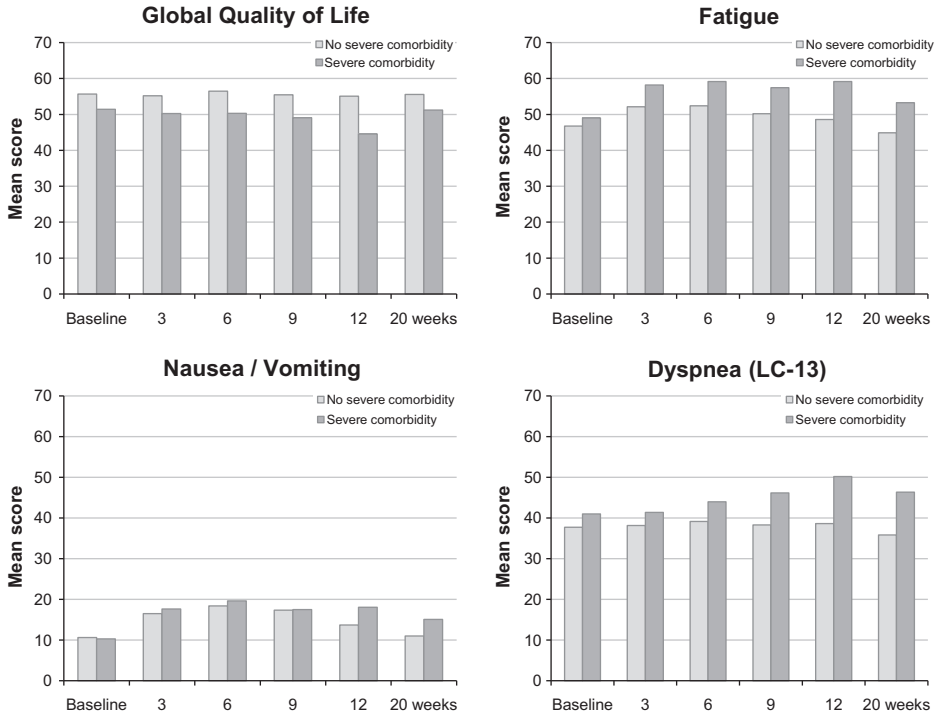

Fig. 4 – Mean scores for the primary HRQoL-end-points. A higher score on functional scales (global QoL) represents a better HRQoL, whereas a higher score on the symptom-scales (fatigue, nausea/vomiting and dyspnoea) represents more symptoms and poorer HRQoL. The minimum difference in mean scores to show a clinically relevant difference in HRQoL was defined as 10 points.

elderly (⩾70 years) receiving non-platinum-chemotherapy[15] and elderly (⩾65 years) receiving platinum-chemotherapy.[16]

A possible explanation why comorbidity does not appear to be a prognostic factor in advanced NSCLC is given by Read and colleagues.[12] They analysed patients with breast, colon, lung and prostate cancer, and found that the influence of comorbidity on survival is relative to the prognosis of the malignant disease. Whereas comorbidity was a prognostic factor for survival in patients with a long life expectancy, this was not the case in cohorts with a poor prognosis (such as metastastic lung cancer). These patients seem to die from their cancer before other disorders worsen enough to influence survival.

The most important result of the toxicity analyses was that patients with severe comorbidity acquired more fevers when neutropenic and all patients who died from neutropenic infections in our trial had such disorders – mainly in the cardiovascular and respiratory systems. There were also more deaths from other adverse events during the treatment period among these patients, but despite this fact, they did not have a significantly shorter survival. Otherwise, the patients with severe comorbidity did not have more clinically relevant toxicity.

The results from other studies of toxicity in relation to comorbidity are not consistent,[13,16,17] possibly due to small sample sizes and differences in pharmacological profile and intensity of the chemotherapy administered. However, the association between comorbidity and the risk of infection in lung cancer patients has been demonstrated in a previous trial,[13] and studies of patients with several types of cancers have shown that comorbidity increases the risk for complications from neutropenic infections.[28,29] From a clinical point of view it seems reasonable that patients with cardiovascular and respiratory disease may have a higher risk of developing infections when neutropenic. Our results suggest that these patients should be monitored closely during treatment. If our observations are confirmed, randomised studies investigating whether prophylactic antibiotics or use of granulocyte colony stimulating agents can prevent infections in patients with severe comorbidity may be warranted. Withholding chemotherapy from all the patients with severe comorbidity (they accounted for 40% of the study population) does not seem to be a reasonable precaution to avoid neutropenic infections among a few; particularly since their overall survival was not significantly inferior to those without such comorbidity.

The patients with severe comorbidity reported poorer HRQoL and they had slightly more deterioration than the patients with less comorbidity. We find that these differences are too small to suggest that life-prolonging therapy should be withheld from these patients. There are no entirely relevant reports to support our conclusion, but in a study of head and neck cancer, patients with severe comorbidity had inferior HRQoL before, but not after radiotherapy.[30]

One possible limitation to our study is that all comorbidities may not have been registered in the hospital medical records. The prevalence of severe comorbidity in our population is, however, comparable to what has been registered in other studies of NSCLC-patients.[7,12–15] If minor comorbidites have not been registered, that would mostly influence the severity index – which was not associated with inferior survival, more

toxicity or worse HRQoL in our study population. From a clinical point of view it seems unlikely that minor comorbidities should influence these outcomes. The sample size is large, and we find that the study population is quite representative for the patients seen in the everyday clinic; a large proportion had PS 2, and even if elderly are underrepresented also in our trial, more than one third was >70 years. It is to be noted, though, that adequate liver and kidney function was required for study inclusion, and we do not have information about the patients who were not enrolled; some patients may have been considered ineligible due to comorbidity despite the eligibility criteria.

The CIRS-G is one of the most commonly used instruments for measuring comorbidity, it is comprehensive and has good inter-rater and test–retest reliability.[21] Compared with the Charlson index, the most popular instrument for measuring comorbidity, the CIRS-G is more sensitive and it includes assessment of non-lethal conditions. Accordingly, in two studies of NSCLC, CIRS-G scores but not Charlson scores were significant prognostic factors.[9,10]

In conclusion, the results of our study suggest that advanced NSCLC-patients with severe comorbidity appear to have a higher risk of complications when neutropenic and should be monitored closely. Otherwise, they seem to benefit from and tolerate platinum-based chemotherapy as well as other patients.

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