Health-related quality of life in elderly patients with advanced non-small cell lung cancer comparing carboplatin and weekly paclitaxel doublet chemotherapy with monotherapy

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ABSTRACT In the *Intergroupe Francophone de Cancérologie Thoracique* 0501 trial the carboplatin-paclitaxel chemotherapy increased toxicity (most frequent, decreased neutrophil count, asthenia). We longitudinally compared health-related quality of life (HRQoL) of the two treatment arms.

In total, 451 patients aged 70–89 years with advanced non-small cell lung cancer (NSCLC) were randomly assigned to receive carboplatin plus paclitaxel or vinorelbine or gemcitabine. HRQoL was assessed by means of the European Organisation for Research and Treatment of Cancer QLQ-C30 questionnaire at baseline, week 6 and week 18.

Using a five-point decrease as the minimal clinically important difference, patients treated with the chemotherapy doublet exhibited a significant longer time until definitive deterioration (TUDD) for two HRQoL dimensions: physical functioning (median TUDD: 2.04 for the doublet *versus* 1.71 months for monotherapy; log-rank p=0.01) and nausea and vomiting (median: not reached *versus* 4.83, respectively; log-rank p=0.046). Cox multivariate analysis revealed the carboplatin and paclitaxel arm to be independently associated with longer TUDD for these two HRQoL dimensions. In addition, TUDD didn't significantly differ between the two arms for all the other HRQoL dimensions.

The chemotherapy doublet did not reduce TUDD in elderly patients with advanced NSCLC. Moreover, TUDD was prolonged for two HRQoL dimensions, namely physical functioning and nausea and vomiting.

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Introduction

Increases in life expectancy and the strong association of lung cancer frequency with ageing have led to a significant rise of this cancer type in the elderly. In a community hospital-based survey in France, patients aged 70 years and over, presenting with pathological confirmed lung cancer, represented 32% of the total 5667 patients recorded during year 2000, and those aged over 80 years represented 18.1% [1, 2].

Between 2006 and 2009, the *Intergroupe Francophone de Cancérologie Thoracique* (IFCT; French Intergroup of Thoracic Oncology) conducted a phase III trial (IFCT-0501 trial) involving elderly patients with advanced non-small cell lung cancer (NSCLC) in order to compare the carboplatin and weekly paclitaxel doublet regimen to single-agent chemotherapy with gemcitabine or vinorelbine [3]. Median overall survival was 10.3 months for the doublet and 6.2 months for the monotherapy (hazard ratio 0.64, 95% CI 0.52–0.78; p<0.0001). Several grade 3–4 adverse events were, however, found to be significantly increased in the doublet arm, namely neutropenia, febrile neutropenia, anaemia, thrombocytopenia, asthenia and sensory neuropathy. Since this study was published, the European Society for Medical Oncology (ESMO) [4] and the National Comprehensive Cancer Network (NCCN) [5] have recommended platinum-based chemotherapy as the preferred option for patients aged 70 years or over with a performance status of 0–1, as well as selected performance status 2 patients with adequate organ function. A single-agent approach may still be the recommended treatment for unfit or comorbid patients who are more likely to suffer from significantly more treatment-related adverse events [6].

Health-related quality of life (HRQoL) reflects the patient-perceived evaluation of one's health, including physical, emotional and social dimensions as well as symptoms due to disease or treatment. The Food and Drug Administration considers HRQoL to be a significant endpoint for assessing direct clinical benefits for the patients [7, 8]. Some publications have focused on the comparison between patient and clinician reporting of the treatment-related adverse events experienced by cancer patients, which have demonstrated underreporting of adverse events by clinicians [9–12].

Therefore, given the slight increase in adverse event frequency observed in the IFCT-0501 trial, we sought to longitudinally compare HRQoL scores between both treatment arms of the IFCT-0501 trial [13].

Methods

Patients and study design

Patients were eligible if they were aged 70–89 years and presented with stage IV NSCLC or a stage III disease unsuitable for radical radiation therapy and a performance status ⩽2. Patients were randomly assigned 1:1 (minimisation) to either four 4-week cycles of carboplatin (day 1) plus paclitaxel (days 1, 8 and 15) or five 3-week cycles of vinorelbine or gemcitabine (days 1 and 8). The protocol was approved by the *Comité de Protection des Personnes* (a French research ethics board) of Ile-de-France Aulnay-sous-Bois, France. The trial was authorised by the French National Authority for Health. All enrolled patients provided written informed consent. The study design has been described in detail in a previous publication [3].

Health-related quality of life

HRQoL was a secondary endpoint of the trial, assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 [14] at randomisation and then again at 6 and 18 weeks. Additional questionnaires were given to 65 (28.6%) patients in the monotherapy arm and 88 (39.2%) in the doublet chemotherapy arm at 12 weeks after randomisation, the results of which were included in the analysis. The questionnaires were filled in by the patients themselves at the hospital on paper prior to a medical visit.

The QLQ-C30 is a cancer-specific tool composed of 30 items [15–17], allowing to assess five functional scores (physical, role, cognitive, social and emotional), a global quality-of life-score and nine symptom scores (nausea and vomiting, pain, fatigue, dyspnoea, sleeping disturbances, appetite loss, constipation, diarrhoea and financial difficulties) [14]. These scores were generated according to the EORTC Scoring Manual and thus were standardised on a 0 to 100 scale in order that a high score reflects a high functional level, a high global quality of life level and a high symptomatic level [18]. If at least half of the items of one given dimension were completed, the score could be estimated considering that missing items did not differ from items answered (corresponding to simple imputation by the mean). If more than half of the items were missing, the score could not be computed and thus was missing.

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Statistical methods

All analyses were performed according to the modified intention-to-treat (ITT) principle, *i.e.* an ITT population with at least one available baseline HRQoL questionnaire.

To determine the profile of baseline missing HRQoL data, patients who entirely completed the baseline HRQoL questionnaire (*i.e.* with all items completed) were compared with other patients (*i.e.* those with at least one missing item at baseline) according to primary clinical and medical patients characteristics collected at baseline. Qualitative/categorical variables have been described using frequencies and percentages and then being compared by group (*i.e.* according to the availability or not of the baseline HRQoL questionnaire and then according to treatment arm) using the Chi-squared or Fisher's exact testwhen expected numbers were less than 5%. Continuous/quantitative variables were described using mean±SD or median (range) and compared by group using a t-test or the Mann–Whitney non-parametric test if a normal distribution of the variable was not respected.

The minimal clinically important difference (MCID) for HRQoL scores was fixed to 5 points [19, 20]. The time until definitive HRQoL score deterioration (TUDD) of a score was defined as the interval between randomisation and the deterioration ⩾5 points in the QLQ-C30 score compared to the HRQoL score at baseline, with no further improvement in HRQoL score ⩾5 points or if a patient dropped out after this decrease, resulting in missing data. Patients were censored at the last follow-up when no deterioration in HRQoL score compared with baseline was observed or in cases where a deterioration was observed but followed by a significant improvement in HRQoL score compared to baseline. Patients with a baseline score but no follow-up score have been included in the analysis, though, were censored immediately after baseline.

The TUDD curves were calculated using the Kaplan–Meier estimation and described using medians and 95% confidence interval. TUDD curves were compared using log-rank tests. The univariate Cox model was applied to calculate the HR with its 95% confidence interval. We assessed the following variables: treatment arm, age, sex, performance status, smoking status, mini-mental state (MMS) examination score, activities of daily living (ADL) questionnaire score, Charlson comorbidity index (CCI) score, body mass index (BMI), disease stage and histology [3]. All variables with a p-value <0.1 were included in a multivariate Cox regression model in order to identify factors independently associated with TUDD.

We performed sensitivity analyses with the aim of evaluating the different definitions of TUDD. These analyses were repeated with 10-point differences in scores for the MCID.

The analysis was conducted according to the patient-reported outcomes CONSORT (Consolidated Standards of Reporting Trials) statement [21].

A p-value of 0.05 or lower was considered statistically significant. All analyses were performed using SAS software, Version 9.3 (SAS Institute), and R software (Version 2.10.1).

Results

Patients

Between April 2006 and December 2009, 451 patients were enrolled. Of them, 226 were assigned single-agent chemotherapy (62 with vinorelbine and 164 with gemcitabine) and 225 received doublet chemotherapy [3].

HRQoL compliance and scores at baseline

The total number of patients who completed the entire questionnaire was 361 (80.04%) at baseline, 191 (50.9%) at 6 weeks, 69 (25.6%) at 12 weeks, and 86 (39.1%) at 18 weeks.

No difference was observed in terms of baseline characteristics of the patients between patients who completed the entire baseline HRQoL questionnaire and those who did not, suggesting that baseline missing data could be considered as missing completely at random (table 1). The mean HRQoL scores at baseline were similar between the two treatment arms (table 2).

The total number of available questionnaires (*i.e.* the number of questionnaires with at least one score of HRQoL that could be calculated) was 421 at baseline, 315 (74.8%) at 6 weeks, 153 (36.3%) at 12 weeks, and 250 (53.4%) at 18 weeks (figure 1).

TUDD with a MCID >5 points

The results in table 3 showed that the TUDD with an MCID ⩾5 points in HRQoL score was significantly longer under the chemotherapy doublet compared with monotherapy for two HRQoL dimensions: physical functioning and nausea and vomiting.

TABLE 1 Patient characteristics according to the completion of the baseline EORTC QLQ-C30

	Questionnaire complete at baseline	Questionnaire not complete at baseline	Fisher exact test p-value
Patients n	361	90	
Age years			
<77	180 (49.9)	48 (53.3)	0.56
⩾77	181 (50.1)	42 (46.7)	
Sex			
Male	270 (74.8)	63 (70.0)	0.35
Female	91 (25.2)	27 (30.0)	
Performance status			
0–1	267 (74.0)	63 (70.0)	0.15
2	93 (25.7)	27 (30.0)	
Unknown	1 (0.3)	0 (0)	
Smoking status			
Never smoked	73 (20.2)	21 (23.3)	0.51
Ever smoked	288 (80.0)	69 (76.7)	
MMS			
⩽20	29 (8.0)	6 (6.7)	0.82
>20	330 (91.4)	76 (84.4)	
Unknown	2 (0.6)	8 (8.9)	
ADL			
<6	66 (18.3)	22 (24.4)	0.12
6	288 (79.8)	62 (68.9)	
Unknown	7 (1.9)	6 (6.7)	
CCI			
⩽2	268 (74.2)	73 (81.1)	0.17
>2	93 (25.8)	17 (18.9)	
BMI			
⩽20	43 (11.9)	9 (10.0)	0.77
20<BMI⩽30	276 (76.5)	72 (80.0)	
>30	42 (11.6)	9 (10.0)	
Stage			
IIIA–IIIB	70 (19.4)	17 (18.9)	0.90
IV	291 (80.6)	73 (81.1)	
Histology			
Adenocarcinoma	184 (51.0)	45 (50.0)	0.63
Squamous	123 (34.0)	28 (31.1)	
Other	54 (15.0)	17 (18.9)	

Data are presented as n (%), unless otherwise stated. MMS: mini-mental state; ADL: activities of daily life; CCI: Charlson's comorbidity index; BMI: body mass index.

For the physical functioning score, 72 patients in the doublet arm and 91 in the single-agent arm experienced a definitive deterioration ⩾5 points. The median TUDD was 2.04 months (95% CI 1.87–3.88) and 1.71 months (95% CI 1.58–1.91), respectively (HR 0.67, 95% CI 0.49–0.91; p=0.01) (figure 2a). Cox multivariate analysis revealed that the carboplatin and paclitaxel doublet was independently associated with longer TUDD for the physical functioning dimension (HR 0.57, 95% CI 0.42–0.78; p=0.0079) (table 4).

For the nausea and vomiting score, 10 and 19 patients experienced a definitive deterioration ⩾5 points in each arm, respectively. Median TUDD was not reached (NR) in the doublet arm and was 4.83 months (95% CI 4.70–NR) in the monotherapy arm (HR 0.46, 95% CI 0.21–1.00; p=0.046) (figure 2b). Cox multivariate analysis revealed that the carboplatin and paclitaxel doublet was independently associated with longer TUDD for the nausea and vomitting dimension (HR 0.39, 95% CI 0.18–0.87; p=0.02) (table 5).

For two other dimensions, namely fatigue (FA) and social functioning (SF), TUDD was longer for the chemotherapy doublet arm, with borderline significance. For the fatigue score, 33 patients in the doublet chemotherapy group and 44 in the monotherapy group experienced a definitive deterioration ⩾5 points. The median TUDD was 5.03 months (95% CI 4.44–NR) in the chemotherapy doublet arm and 4.37 months (95% CI 4.24–4.80) in the monotherapy arm (HR 0.65, 95% CI 0.41–1.03; p=0.06). Cox multivariate analysis demonstrated a trend towards longer TUDD for the fatigue dimension with the carboplatin and paclitaxel doublet (HR 0.67, 95% CI 0.42–1.05; p=0.08) (supplementary table S1).

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TABLE 2 Health-related quality of life scores at baseline by treatment arm

QLQ-C30 scores	Monotherapy group (n=226)			Doublet chemotherapy group (n=225)			p-value
	n	Mean±SD	Median (range)	n	Mean±SD	Median (range)	
Global quality of life	214	55.4±18.4	58.3 (8.3–100)	206	58.2±19	58.3 (16.7–100)	0.12
Physical functioning	214	69.1±22.5	73.3 (6.7–100)	206	69.3±22.5	73.3 (0–100)	0.95
Role functioning	214	63±35.7	66.7 (0–100)	206	69.1±32.3	75 (0–100)	0.068
Emotional functioning	213	71.3±21.3	75 (0–100)	207	73.1±23	75 (0–100)	0.42
Cognitive functioning	214	81.2±21.9	83.3 (0–100)	207	83.7±20.2	83.3 (0–100)	0.2
Social functioning	209	75.6±31.8	100 (0–100)	202	80.4±29	100 (0–100)	0.11
Fatigue	213	45.5±28	33.3 (0–100)	207	41.4±27.6	33.3 (0–100)	0.14
Nausea and vomiting	214	5.4±14.5	0 (0–100)	207	5.6±14.6	0 (0–100)	0.86
Pain	214	29±29.8	16.7 (0–100)	206	26.7±29.9	16.7 (0–100)	0.44
Dyspnoea	213	47.4±34.1	33.3 (0–100)	206	40.8±35.1	33.3 (0–100)	0.050
Sleeping disturbances	214	29.8±32	33.3 (0–100)	206	28±32.8	33.3 (0–100)	0.58
Appetite loss	213	34.7±29.7	33.3 (0–100)	206	36.9±31.8	33.3 (0–100)	0.55
Constipation	214	24.9±32.2	0 (0–100)	206	26.2±31.8	0 (0–100)	0.68
Diarrhoea	211	7.3±18.1	0 (0–100)	206	7.8±18.7	0 (0–100)	0.78
Financial difficulties	212	5.2±16.5	0 (0–100)	204	3.6±13.6	0 (0–100)	0.28

For the SF dimension, 55 patients in the doublet chemotherapy group and 65 in the monotherapy group experienced a definitive deterioration ⩾5 points. The median TUDD was 4.21 months (95% CI 2.33–4.37) in the chemotherapy doublet arm and 1.91 months (95% CI 1.74–4.01) in the monotherapy arm (HR 0.73, 95% CI 0.51–1.05; p=0.049). Cox multivariate analysis revealed that the carboplatin and paclitaxel doublet

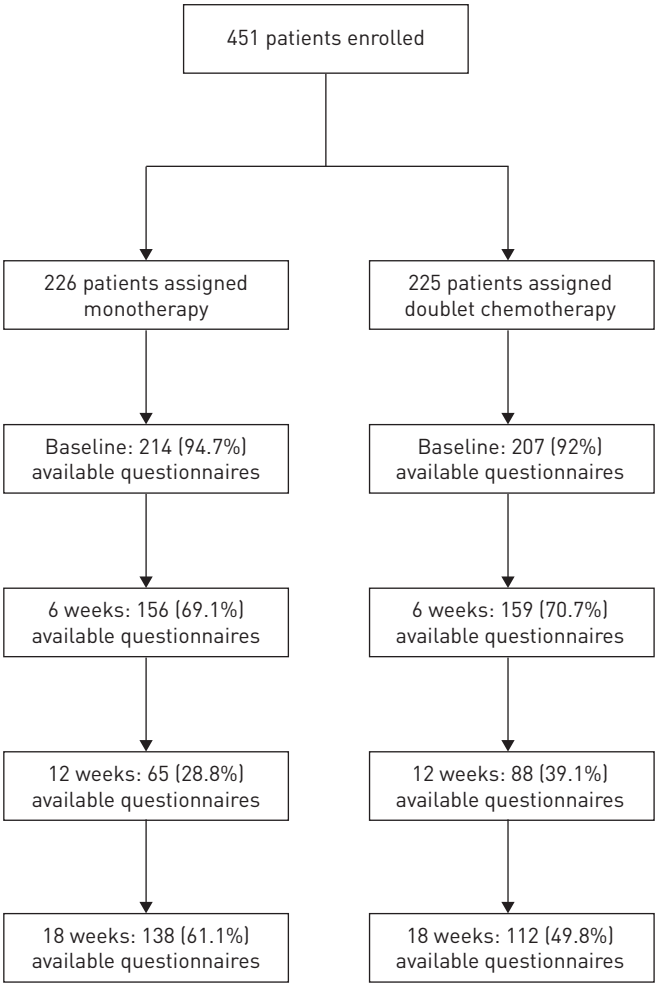

FIGURE 1 Number of available questionnaires (*i.e.* the number of questionnaires with at least one score of health related quality of life that can be calculated).

TABLE 3 Time until definitive deterioration with minimal clinically important difference ⩾5 points and 10 points according to treatment arm

	MCID ⩾5 points			MCID ⩾10 points		
	Events	Median (95% CI) TUDD months	Log-rank p-value	Events	Median (95% CI) TUDD months	Log-rank p-value
Global quality of life						
Monotherapy	73	1.91 (1.71–4.01)	0.35	51	4.24 (3.98–NR)	0.84
Doublet chemotherapy	69	2.33 (1.87–4.21)		52	4.27 (2.33–NR)	
Physical functioning						
Monotherapy	91	1.71 (1.58–1.91)	**0.010**	70	2.14 (1.74–4.17)	0.23
Doublet chemotherapy	72	2.04 (1.87–3.88)		64	3.81 (2.04–4.21)	
Role functioning						
Monotherapy	59	3.98 (1.91–4.50)	0.94	59	3.98 (1.91–4.50)	0.94
Doublet chemotherapy	66	3.68 (1.94–4.14)		66	3.68 (1.94–4.14)	
Emotional functioning						
Monotherapy	49	4.24 (3.19–NR)	0.32	40	NR (3.88–NR)	0.27
Doublet chemotherapy	45	4.40 (4.04–NR)		35	4.53 (4.37–NR)	
Cognitive functioning						
Monotherapy	55	4.24 (1.91–4.67)	0.75	55	4.24 (1.91–4.70)	0.75
Doublet chemotherapy	58	4.14 (3.71–4.53)		58	4.14 (3.71–4.53)	
Social functioning						
Monotherapy	65	1.91 (1.74–4.01)	**0.09**	65	1.91 (1.74–4.01)	0.09
Doublet chemotherapy	55	4.21 (2.33–4.37)		55	4.21 (2.33–4.37)	
Fatigue						
Monotherapy	44	4.37 (4.24–4.80)	0.06	44	4.37 (4.24–4.80)	**0.05**
Doublet chemotherapy	33	5.03 (4.44–NR)		32	5.03 (4.44–NR)	
Nausea and vomiting						
Monotherapy	19	4.83 (4.70–NR)	**0.046**	19	4.83 (4.70–NR)	**0.046**
Doublet chemotherapy	10	NR (5.03–NR)		10	NR (5.03–NR)	
Pain						
Monotherapy	50	4.30 (4.01–4.83)	0.16	50	4.30 (4.01–4.83)	0.10
Doublet chemotherapy	40	NR (4.24–NR)		40	NR (4.23–NR)	
Dyspnoea						
Monotherapy	42	4.50 (4.14–4.86)	0.40	42	4.50 (4.14–4.86)	0.40
Doublet chemotherapy	51	4.07 (2.27–5.03)		51	4.07 (2.27–5.03)	
Sleeping disturbances						
Monotherapy	41	4.83 (4.14–4.83)	0.27	41	4.83 (4.14–4.83)	0.27
Doublet chemotherapy	33	NR (4.30–NR)		33	NR (4.31–NR)	
Appetite loss						
Monotherapy	36	4.66 (4.24–4.83)	0.93	36	4.67 (4.24–4.83)	0.93
Doublet chemotherapy	40	4.86 (4.01–NR)		40	4.86 (4.01–NR)	
Constipation						
Monotherapy	28	4.67 (4.37–NR)	0.79	28	4.67 (4.37–NR)	0.79
Doublet chemotherapy	35	5.03 (4.37–NR)		35	5.03 (4.37–NR)	
Diarrhoea						
Monotherapy	16	4.83 (4.67–NR)	0.25	16	4.83 (4.67–NR)	0.25
Doublet chemotherapy	12	NR (NR–NR)		12	NR (NR–NR)	
Financial difficulties						
Monotherapy	10	NR (4.83–NR)	0.31	10	NR (4.83–NR)	0.32
Doublet chemotherapy	6	NR (NR–NR)		6	NR (NR–NR)	

NR: not reached.

prolonged TUDD for the SF dimension, although only with borderline statistical significance (HR 0.71, 95% CI 0.49–1.02; p=0.06) (supplementary table S2).

For the other HRQoL dimensions, the chemotherapy doublet arm did not alter TUDD, compared with monotherapy.

Sensitivity analyses

Table 3 shows the results with a MCID ⩾10 points in HRQoL score.

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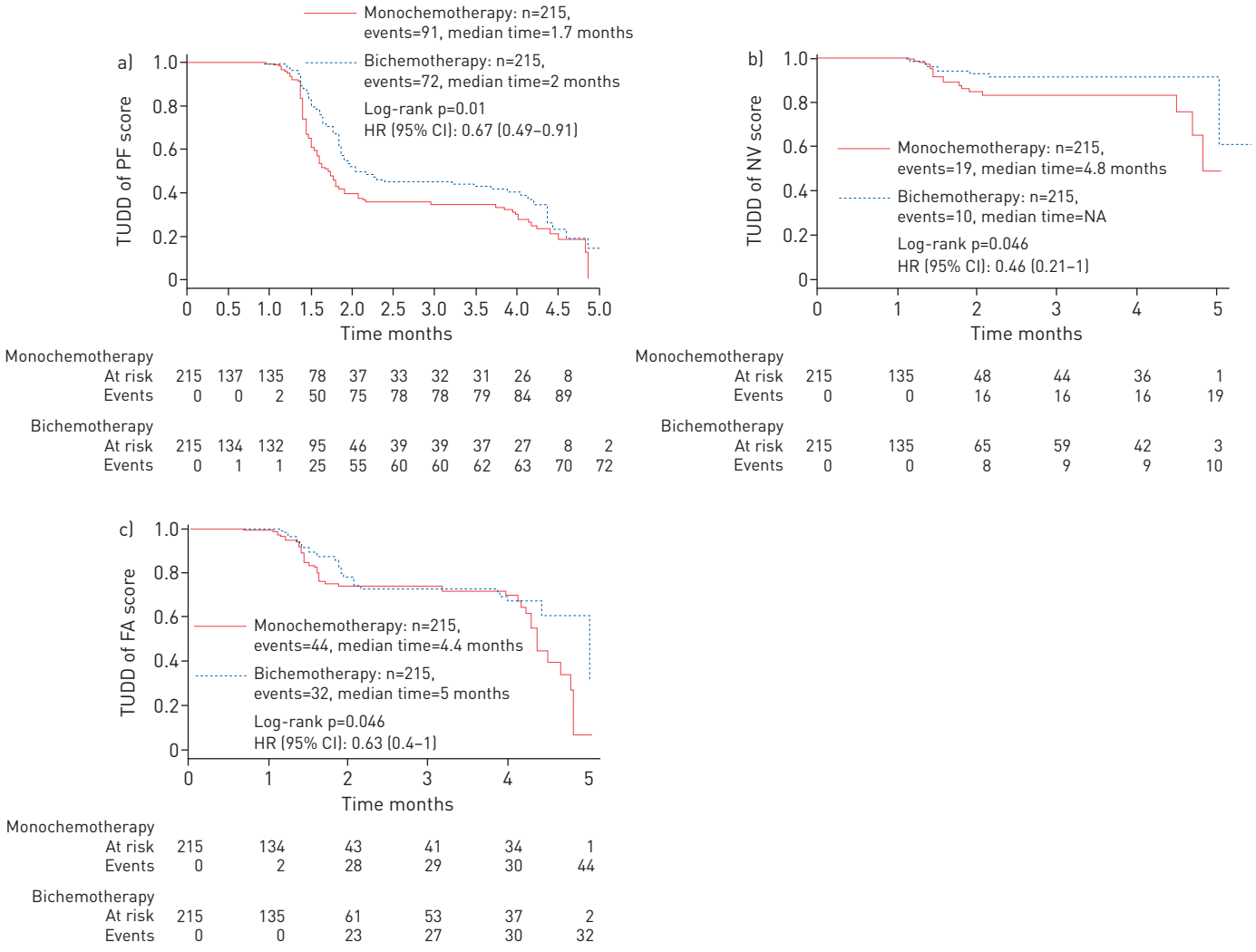

FIGURE 2 a) Time until definitive deterioration (TUDD) of physical functioning (PF) score according to treatment arm (Kaplan–Meier estimation) with minimal clinically important difference (MCID) ⩾5. b) TUDD of nausea and vomiting (NV) score according to treatment arm (Kaplan–Meier estimation) with MCID ⩾5 points. c) TUDD of fatigue (FA) score according to treatment arm (Kaplan–Meier estimation) with MCID ⩾10 points.

TUDD was significantly longer under the doublet when compared with single-agent chemotherapy for the FA dimension. For the FA score, 32 patients in the doublet chemotherapy arm and 44 in the monotherapy arm experienced a definitive deterioration ⩾10 points. The median TUDD was 5.03 months (95% CI 4.44 months–NR) in the doublet chemotherapy arm and 4.37 months (95% CI 4.24–4.80 months) in the monotherapy arm (HR 0.63; 95% CI 0.40–0.99; p=0.046) (figure 2c). Cox multivariate analysis once more demonstrated that the carboplatin and paclitaxel doublet was independently associated with longer TUDD for the FA dimension (HR 0.60; 95% CI 0.49–0.74; p<0.001) (table 6).

Similar results to the primary analysis were observed for the other dimensions.

Discussion

The IFCT-0501 trial demonstrated that, when compared to a monotherapy regimen, the carboplatin/paclitaxel therapy combination improved overall survival in elderly patients with advanced NSCLC. However, the safety of carboplatin/paclitaxel was slightly less favourable than that of monotherapy. Studies have revealed that most oncologists and patients are unwilling to prolong survival at the expense of worsening HRQoL [22, 23]. It was therefore important to assess the HRQoL results as a secondary endpoint in the IFCT-0501 trial. Our study highlighted that TUDD values with an MCID ⩾5 points in HRQoL scores were significantly longer with doublet chemotherapy than with monotherapy for two HRQoL dimensions, namely physical functioning and nausea and vomiting. Moreover, for two other dimensions, SF and FA, TUDD was favoured by the chemotherapy doublet, though with borderline

TABLE 4 Cox analysis of time until definitive deterioration for physical functioning dimension with minimal clinically important difference ⩾5

	Patients n	Events n	Univariate analysis (n=430)		Multivariate analysis (n=430)	
			HR (95% CI)	p-value	HR (95% CI)	p-value
Total		163				
Sex						
Male	317	110	1.00		1.00	
Female	113	53	1.37 (0.98–1.90)	**0.065**	1.53 (1.09–2.15)	**0.013**
Age years						
<77	218	84	1.00			
⩾77	212	79	0.83 (0.61–1.13)	0.24		
Treatment						
Monotherapy	215	91	1.00		1.00	
Doublet chemotherapy	215	72	0.67 (0.49–0.91)	**0.01**	0.57 (0.42–0.78)	**0.008**
Performance status score						
0–1	312	127	1.00			
2	117	36	1.25 (0.86–1.81)	0.24		
Smoking status						
Never smoker	91	45	1.00			
Ever smoker	339	118	0.77 (0.55–1.10)	0.15		
Disease stage						
III	82	31	1.00			
IV	348	132	1.09 (0.74–1.62)	0.65		
Histology						
Adenocarcinoma	218	87	1.00			
Squamous	146	48	1.04 (0.73–1.49)			
Other	66	28	0.99 (0.65–1.53)	0.97		
MMS						
⩽20	33	9	1.00			
>20	393	152	0.99 (0.50–1.94)	0.96		
ADL						
<6	83	27	1.00			
6	339	132	0.75 (0.49–1.13)	0.17		
CCI						
⩽2	321	116	1.00		1.00	
>2	109	47	1.63 (1.16–2.29)	**0.005**	1.50 (1.08–1.12)	**0.002**
BMI						
⩽20	48	15	1.00			
20<BMI⩽30	332	127	0.88 (0.51–1.50)			
>30	50	21	0.72 (0.37–1.40)	0.59		

MMS: mini-mental state examination questionnaire; ADL: activities of daily living questionnaire; CCI: Charlson's comorbidity index; BMI: body mass index.

significance. Finally, no difference in TUDD was observed for the other HRQoL dimensions when comparing the two treatment arms. For the FA dimension, TUDD with an MCID ⩾5 points was not prolonged in the doublet arm compared with monotherapy, while the TUDD with an MCID ⩾10 points was significantly longer. This could be accounted for by the observation that one patient in the doublet chemotherapy arm exhibited a deterioration of between 6 and 10 points, leading to 32 events using the MCID ⩾10 points and 33 using an MCID ⩾5 points. For the physical functioning dimension, TUDD with an MCID ⩾10 points was no longer significantly increased under the doublet chemotherapy. This could be explained by the fact that less patients exhibited deterioration with an MCID ⩾10 points (64 and 70 for the doublet chemotherapy and monotherapy arm, respectively) compared with an MCID ⩾5 points (72 and 91 for the doublet chemotherapy and monotherapy arm, respectively).

These results suggest that, despite the moderately increased toxicity induced by the chemotherapy doublet, TUDD was, in fact, longer in patients treated with the chemotherapy doublet for the four following HRQoL dimensions: physical functioning, which assesses self-care, mobility and physical activity; SF, which measures how patients can perform their usual work and housework activities; FA; and nausea and vomiting.

Interestingly, we observed significantly more Grade 3 and 4 asthenia with the doublet, while the FA dimension was independently associated with longer TUDD for the carboplatin and paclitaxel arm compared with that

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TABLE 5 Cox analysis of time until definitive deterioration for nausea and vomiting dimension with minimal clinically important difference ⩾5 points and with minimal clinically important difference ⩾10 points

	Patients n	Events n	Univariate analysis (n=430)		Multivariate analysis (n=430)	
			HR (95% CI)	p-value	HR (95% CI)	p-value
Total		29				
Sex						
Male	317	15	1.00		1.00	
Female	113	14	2.42 (1.17–5.02)	**0.017**	2.06 (0.67–6.32)	0.21
Age years						
<77	218	15	1.00			
⩾77	212	14	0.98 (0.47–2.04)	0.96		
Treatment						
Monotherapy	215	19	1.00		1.00	
Doublet chemotherapy	215	10	0.46 (0.21–1.00)	**0.05**	0.39 (0.18–0.87)	**0.02**
Performance status score						
0–1	312	21	1.00			
2	117	8	1.44 (0.62–3.32)	0.38		
Smoking status						
Never smoker	91	12	1.00		1.00	
Ever smoker	339	17	0.47 (0.23–0.99)	**0.048**	1.00 (0.33–3.03)	0.99
Disease stage						
III	82	3	1.00			
IV	348	26	1.96 (0.59–6.51)	0.27		
Histology						
Adenocarcinoma	218	18	1.00			
Squamous	146	6	0.60 (0.24–1.52)			
Other	66	5	0.86 (0.32–2.32)	0.56		
MMS						
⩽20	33	3	1.00			
>20	393	27	0.75 (0.18–3.17)	0.70		
ADL						
<6	83	10	1.00		1.00	
6	339	19	0.31 (0.14–0.67)	**0.003**	0.36 (0.16–0.83)	**0.02**
CCI						
⩽2	321	23	1.00			
>2	109	6	0.88 (0.36–2.18)	0.78		
BMI						
⩽20	48	4	1.00			
20<BMI⩽30	332	20	0.49 (0.17–1.45)			
>30	50	5	0.82 (0.22–3.08)	0.32		

MMS: mini-mental state; ADL: activities of daily life; CCI: Charlson's comorbidity index; BMI: body mass index.

achieved with monotherapy. There are several possible explanations for this apparent contradiction. Firstly, the toxic effects were assessed by the incidence of Grade 3 and 4 toxicities, according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (version 3.0), while the TUDD of an HRQoL dimension used a longitudinal approach with a 5- or 10-point MCID. Secondly, the adverse events were evaluated by the physician rather than being self-reported [24–26]. While Grade 3 and 4 nausea and vomiting were reported in 2.7% and 0.9% of the patients in the doublet chemotherapy and monotherapy arms, respectively, TUDD was longer for the carboplatin and paclitaxel arm regarding the nausea and vomiting dimension, compared with the monotherapy arm. Besides the above potential explanations, the nausea and vomiting could also be attributed either directly to the cancer or to other treatments administered for managing cancer-related pain, such as morphine analogues.

One other trial, the Multicenter Italian Lung Cancer in the Elderly Study (MILES) study, analysed HRQoL in elderly NSCLC patients treated with a chemotherapy doublet (combination of vinorelbine plus gemcitabine) compared with single agents (vinorelbine or gemcitabine alone). The authors observed no statistically significant differences in terms of HRQoL between the patients assigned to combination treatment and those assigned to single-drug treatments [27]. Nevertheless, the statistical method used was a simple change-from-baseline approach. The West Japan Thoracic Oncology Group 9904 study compared weekly docetaxel and cisplatin administration *versus* docetaxel monotherapy in elderly patients with advanced NSCLC. This study failed to demonstrate any survival advantage of weekly docetaxel plus

TABLE 6 Cox analysis of time until definitive deterioration for fatigue dimension with minimal clinically important difference ⩾10 points

	Patients n	Events n	Univariate analysis (n=430)		Multivariate analysis (n=430)	
			HR (95% CI)	p-value	HR (95% CI)	p-value
Total		76				
Sex						
Male	317	50	1.00			
Female	113	26	1.28 (0.80–2.06)	0.31		
Age years						
<77	218	38	1.00			
⩾77	212	38	0.95 (0.60–1.48)	0.81		
Treatment						
Monotherapy	215	44	1.00		1.00	
Doublet chemotherapy	215	32	0.63 (0.40–0.99)	**0.046**	0.60 (0.49–0.74)	**< 0.001**
Performance status score						
0–1	312	60	1.00			
2	117	16	1.08 (0.62–1.88)	0.80		
Smoking status						
Never smoker	91	24	1.00			
Ever smoker	339	52	0.81 (0.50–1.32)	0.40		
Disease stage						
III	82	12	1.00			
IV	348	64	1.32 (0.71–2.45)	0.38		
Histology						
Adenocarcinoma	218	41	1.00			
Squamous	146	22	1.05 (0.63–1.77)			
Other	66	13	1.07 (0.57–1.99)	0.97		
MMS						
⩽20	33	5	1.00			
>0	393	71	0.79 (0.32–1.97)	0.61		
ADL						
<6	83	13	1.00			
6	339	63	0.90 (0.49–1.64)	0.73		
CCI						
⩽2	321	67	1.00		1.00	
>2	109	9	0.49 (0.24–0.98)	**0.044**	1.09 (0.86–1.38)	0.50
BMI						
⩽20	48	11	1.00			
20<BMI⩽30	332	56	0.51 (0.27–0.98)			
>30	50	9	0.48 (0.20–1.17)	0.11		

MMS: mini-mental state; ADL: activities of daily life; CCI: Charlson's comorbidity index; BMI: body mass index.

cisplatin over docetaxel monotherapy. Moreover, HRQoL was not favoured by the doublet chemotherapy [28]. The chemotherapy delivery was inferior in patients receiving the cisplatin–docetaxel combination compared with those treated with single-agent docetaxel, suggesting that a carboplatin-based combination should be recommended in elderly patients.

Time-to-HRQoL score deterioration approaches tend to be extensively used in oncology phase III clinical trials [29–33]. These models have the advantage of producing clinically meaningful results for the clinicians and being less affected by missing data than a classical mixed model of analysis of variance for repeated measures [13]. One limitation of our study consisted of the HRQoL analysis being only a secondary endpoint, with no *a priori* statistical hypothesis allowing for power calculation. Then, the treatment effect on HRQoL was small especially for FA and physical functioning dimensions. This small treatment effect may be explained in part by a lack of statistical power because assessment of HRQoL was conducted four times and there were missing data. Nevertheless, there was a difference of 69 days in the median values of TUDD in the social functioning dimension (borderline significant) which may be clinically interesting for the patient.

Moreover, our study shows that the chemotherapy doublet arm did not alter TUDD, compared with monotherapy. Therefore, these findings provide added support for the benefit of doublet chemotherapy in this palliative patient population which can help clinicians in decision making.

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In conclusion, this study showed that, compared with vinorelbine or gemcitabine monotherapy, carboplatin–paclitaxel for elderly patients with advanced NSCLC was associated with a statistically significant longer TUDD for several HRQoL dimensions, while similar TUDD were observed between both treatments for all other HRQoL dimensions. These findings add support for claims of the benefit of the carboplatin weekly paclitaxel doublet chemotherapy in this elderly patient population, proving a significant increase in overall survival. Although at the cost of a slight increase in toxicity, this regimen was proven to induce significant improvement in important HRQoL dimensions and caused no alterations in the other dimensions.

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