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Clinical Studies

Vinorelbine and gemcitabine *vs* vinorelbine and carboplatin as first-line treatment of advanced NSCLC. A phase III randomised controlled trial by the Norwegian Lung Cancer Study Group

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BACKGROUND: Platinum-based doublet chemotherapy is the standard first-line treatment for advanced non-small cell lung cancer (NSCLC), but earlier studies have suggested that non-platinum combinations are equally effective and better tolerated. We conducted a national, randomised study to compare a non-platinum with a platinum combination.

METHODS: Eligible patients had stage IIIB/IV NSCLC and performance status (PS) 0–2. Patients received up to three cycles of vinorelbine $60\,mg\,m^{-2}$ p.o. + gemcitabine $1000\,mg\,m^{-2}$ i.v. day 1 and 8 (VG) or vinorelbine $60\,mg\,m^{-2}$ p.o. day 1 and 8 + carboplatin area under the curve = 5 (Calvert's formula) i.v. day 1 (VC). Patients ⩾75 years received 75% of the dose. Endpoints were overall survival, health-related quality of life (HRQoL), toxicity, and the use of radiotherapy.

RESULTS: We randomised 444 patients from September 2007 to April 2009. The median age was 65 years, 58% were men and 25% had PS 2. Median survival was VG: 6.3 months; VC: 7.0 months, $P = 0.802$. Vinorelbine plus carboplatin patients had more grade III/IV nausea/vomiting (VG: 4%, VC: 12%, $P = 0.008$) and grade IV neutropenia (VG: 7%, VC: 19%, $P < 0.001$). Infections, HRQoL and the use of radiotherapy did not differ significantly between the treatment groups.

CONCLUSION: The two regimens yielded similar overall survival. The VG combination had only a slightly better toxicity profile.

The ideal palliative cancer therapy is effective, harmless and easy to administer. Platinum-based combination chemotherapy is regarded as the standard in first-line therapy in the majority of patients with advanced non-small cell lung cancer (NSCLC). However, benefits in terms of prolonged survival and symptom relief are modest, whereas side effects are common, even when carboplatin is chosen over cisplatin for its favourable toxicity profile (Azzoli *et al*, 2009; Goffin *et al*, 2010). Thus, searching for alternative regimens that might improve health-related quality of life (HRQoL) while maintaining efficacy, is still warranted. An approach is to combine two of the modern third generation non-platinum agents, such as docetaxel, paclitaxel, pemetrexed, vinorelbine, or gemcitabine.

Several randomised controlled trials have compared a platinum combination with vinorelbine and gemcitabine (VG) (Laack *et al*, 2004; Zhang *et al*, 2004; Barlesi and Pujol, 2005; Lilenbaum *et al*, 2005; Tan *et al*, 2005; Yamamoto *et al*, 2006; Greco *et al*, 2007; Han *et al*, 2008; Kubota *et al*, 2008). Most of these studies demonstrated that VG is as effective but less toxic than the respective platinum combinations. One study (Tan *et al*, 2005), however, compared VG with vinorelbine plus carboplatin (VC), both regimens administered in a 3-week schedule to a maximum of six cycles. They found superior survival of 3 months and a more favourable toxicity profile for the VG combination.

As a response to the improved survival by VG over VC presented by Tan *et al* (2005), the Norwegian Lung Cancer Study Group designed a randomised study comparing VG with VC as a first-line treatment in patients with advanced NSCLC. We chose to administer three cycles of chemotherapy, based on the results of three randomised studies assessing the length of therapy in advanced NSCLC (Smith *et al*, 2001; Socinski *et al*, 2002;

von Plessen *et al*, 2006). Further, we chose oral vinorelbine for both treatment arms because of convenient administration, patient preferences, and a similar safety profile as the intravenous formulation (Vokes *et al*, 1994; Liu *et al*, 1997; Jassem *et al*, 2001; Marty *et al*, 2001; Jassem *et al*, 2003; O'Brien *et al*, 2004; Jensen *et al*, 2008).

The primary aim of the study was whether VG is superior to VC with respect to overall survival. Secondary aims were to compare HRQoL, toxicity, and the use of palliative radiotherapy.

PATIENTS AND METHODS

Design and approval

The study was an open, randomised, multicenter phase III trial. It was approved by the Regional Committee for Medical Research Ethics, Western Norway, the Norwegian Social Science Data Services, and the Norwegian Medicines Agency.

Eligibility criteria

Eligible patients had NSCLC stage IV or stage IIIB not eligible for curative treatment, and WHO performance status (PS) 0–2. Patients had to have adequate bone marrow and liver function, no other active malignancy and no gastrointestinal disease affecting absorption of vinorelbine. We allowed inclusion of patients with brain metastases, and defined no upper age limit.

Randomisation

After the patients had signed the informed consent form and completed the baseline HRQoL form, they were randomised by phone to the central study office at Haukeland University Hospital, Bergen, Norway. Randomisation was stratified by WHO PS 0–1 *vs* 2, stage IIIB *vs* IV and age <75 *vs* $\geqslant 75$ years.

Chemotherapy

Both groups were planned for three cycles of chemotherapy in 3-week cycles. Vinorelbine and gemcitabine patients received vinorelbine capsules $60\,\mathrm{mg\,m^{-2}}$ plus intravenous gemcitabine $1000\,\mathrm{mg\,m^{-2}}$, on days 1 and 8. Vinorelbine plus carboplatin patients received carboplatin according to area under the curve $= 5$ (Calvert's formula) on day 1 plus vinorelbine capsules $60\,\mathrm{mg\,m^{-2}}$ on days 1 and 8. The oral dose of vinorelbine $60\,\mathrm{mg\,m^{-2}}$ is comparable with the commonly used intravenous dose of $25\,\mathrm{mg\,m^{-2}}$ (Marty *et al*, 2001). Patients 75 years and older had their doses reduced by 25%. Both groups received prophylactic antiemetics with an intravenous glucocorticoid and 5-HT$_3$-antagonist on day 1, the VG patients also on day 8. Vinorelbine plus carboplatin patients received an oral 5-HT$_3$-antagonist b.i.d. on day 8.

Before the start of each cycle, the absolute neutrophil count (ANC) had to be $\geqslant 1.0 \times 10^9\,\mathrm{l}^{-1}$ and platelets $\geqslant 75 \times 10^9\,\mathrm{l}^{-1}$. The doses were reduced by 25% if ANC was 1.0–$1.49 \times 10^9\,\mathrm{l}^{-1}$, platelets were 75–$99 \times 10^9\,\mathrm{l}^{-1}$, or preceding nadir ANC was $<0.5 \times 10^9\,\mathrm{l}^{-1}$. Doses were reduced by 50% if the nadir platelet count was $<50 \times 10^9\,\mathrm{l}^{-1}$. All dose reductions were maintained for subsequent cycles. Chemotherapy was discontinued if a cycle was delayed by more than 21 days. In cases of neutropenic infections or other grade 3–4 toxicity, chemotherapy was postponed until clinical and haematological recovery and all remaining doses were reduced by 25%. Disease progression, unacceptable toxicity or a patient's request were reasons for discontinuation of the study treatment.

Patient follow-up

All patients underwent a chest X-ray and a CT scan of thorax and upper abdomen before randomisation. Patients were examined clinically and weighed at the start of each treatment cycle. Laboratory tests were performed weekly throughout the treatment period. A chest x-ray was performed at week 9 and every 8 weeks thereafter. Further imaging to determine the disease progression was performed at the treating physician's discretion.

Endpoints

The primary endpoint was overall survival. The secondary endpoints were HRQoL, toxicity and the use of palliative radiotherapy. The prespecified HRQoL analyses were differences between the treatment arms in global QoL and symptom scales for pain, nausea/vomiting, dyspnoea, and fatigue. We defined global QoL at week 9 as the primary HRQoL-endpoint. The study was not designed to assess response rates or time to progression.

Assessment of HRQoL

The patients reported HRQoL on the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 and its lung cancer-specific module LC13 (Aaronson *et al*, 1993). The QLQ-C30 measures fundamental aspects of HRQoL and symptoms commonly reported by cancer patients, whereas the LC13 measures symptoms commonly associated with lung cancer and its treatment. Baseline HRQoL questionnaires had to be completed before randomisation. Follow-up questionnaires were mailed from the study office to the patients' home addresses and were completed immediately before each cycle, 3 weeks after the last cycle, and then every 8 weeks until 57 weeks after the start of treatment. Patients returned the completed forms to the study office in a pre-stamped envelope. Non-responders received one reminder by mail after 14 days.
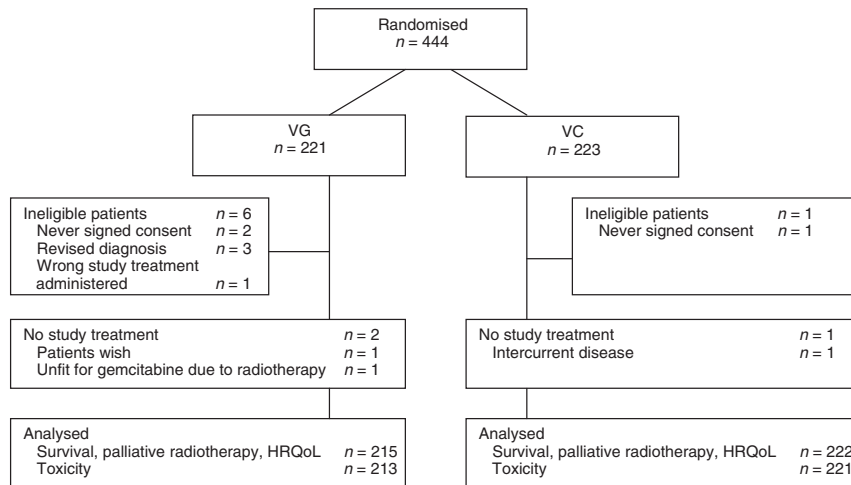
Statistical considerations

We needed 444 patients to detect an increase in 1-year survival from 29 to 40% with 80% power at a 5% significance level, assuming an accrual time of 52 weeks and a minimum follow-up time of 52 weeks. We used the function cpower in Frank Harrell's Hmisc package for R for power calculations (Harrell, 2003). We defined survival time as the time from randomisation until death, and compared the treatment groups with the Kaplan–Meier method and the log-rank test.

Health-related quality of life scores were calculated according to the EORTC QLQ-C30 Scoring Manual (Fayers *et al*, 2001). A high global health status QoL score represents a good QoL, whereas a high symptom-scale score represents more symptoms. Mean scores were calculated for reported values only and compared between the two groups using the Mann–Whitney U-test. We considered a difference in the mean score of >10 points as clinically relevant. Toxicity was categorised according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). The Mann–Whitney U-test was used for group comparisons of haematological toxicity. For analyses of other adverse events and the need for palliative radiotherapy, the χ^2 test was used. The level of significance was defined as $P < 0.05$.

RESULTS

Patients

Between September 2007 and April 2009, 444 patients from 35 Norwegian hospitals were randomised. Seven patients were excluded from all analyses; six because of ineligibility, and one because of administration of the wrong study therapy. Three patients did not receive any study treatment (Figure 1). The analysed patients had, VG *vs* VC respectively, a median age of 65 *vs*

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                         Randomised
                          n = 444
                    ┌─────────┴─────────┐
              ┌─────┴─────┐       ┌─────┴─────┐
              │    VG     │       │    VC     │
              │  n = 221  │       │  n = 223  │
              └───────────┘       └───────────┘
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Ineligible patients	n = 6
Never signed consent	n = 2
Revised diagnosis	n = 3
Wrong study treatment	
administered	n = 1

Ineligible patients	n = 1
Never signed consent	n = 1

No study treatment	n = 2
Patients wish	n = 1
Unfit for gemcitabine due to radiotherapy	n = 1

No study treatment	n = 1
Intercurrent disease	n = 1

Analysed	
Survival, palliative radiotherapy, HRQoL	n = 215
Toxicity	n = 213

Analysed	
Survival, palliative radiotherapy, HRQoL	n = 222
Toxicity	n = 221

Figure 1 CONSORT diagram.

65 years, 41% vs 43% had female gender, 26% vs 25% had PS level 2, 85% vs 85% had disease stage IV, 55% vs 59% had adenocarcinoma, and 5% vs 7% were never smokers (Table 1). We analysed 437 patients for survival, HRQoL and use of palliative radiotherapy, and 434 for toxicity. The survival analysis was finalised in May 2011 after 416 patients had died.

Chemotherapy

The mean number of chemotherapy cycles was (VG vs VC, respectively) 2.6 vs 2.7, while patients ⩾75 years received 2.3 vs 2.7 cycles. The number of patients receiving three cycles without dose reduction was 127 (59%) vs 128 (58%). Study therapy was discontinued due to toxicity in 9 (4%) vs 7 (3%) patients, and due to progressive disease in 24 (11%) vs 25 (11%) patients. Study therapy on day 8 was omitted in 44 of 551 (8%) vs 37 of 593 (6%) cycles.

Overall survival

Overall survival did not differ significantly between the two treatment groups (Figure 2). The median survival time was 6.3 vs 7.0 months (HR = 1.025, CI = 0.85–1.24; $P = 0.802$), with a corresponding 1-year survival rate of 30% vs 27% in the VG and VC arms, respectively.

Good PS and disease stage III were associated with a better prognosis. Median survival was 12.2, 6.8, and 4.3 months for PS 0, 1, and 2, respectively, ($P < 0.001$). Median survival was 9.0, 10.4, and 6.3 months for stage IIIBdry, stage IIIBwet, and stage IV, respectively ($P = 0.036$).

Post-hoc subgroup analyses showed that among patients ⩾75 years ($n = 74$) VG patients had an inferior median survival of 4.6 vs 8.0 months for the VC patients (HR = 1.70, CI = 1.05–2.73; $P = 0.028$), and a corresponding 1-year survival rate of 18% vs 28%. This difference was, however, not statistically significant in a multivariate analysis adjusting for PS level and stage of disease (HR = 1.55, CI = 0.95–2.53). We found no differences in median survival between the treatment arms for patients <75 years (VG: 6.9 months, VC: 6.8 months; HR = 0.89, CI = 0.72–1.10; $P = 0.296$). Age itself was not found to be a significant prognostic factor (<75 years: 6.9 months, ⩾75 years: 6.2 months, $P = 0.066$). Neither did multivariate analysis with interaction test reveal any significant association between age and survival.

We observed no significant differences between treatment arms (VG vs VC, respectively) at any PS level (PS 0: 12.6 vs 11.4 months, $P = 0.208$; PS 1: 6.5 vs 7.0 months, $P = 0.835$; PS 2: 4.0 vs 4.5 months, $P = 0.418$) or stage of disease (IIIBdry: 11.3 vs 7.5 months,

Table 1 Baseline patient characteristics

	VG n = 215		VC n = 222	
	n	**%**	**n**	**%**
Age				
Median	65		65	
Range	44–87		43–83	
⩾75 years	38	18	36	16
Gender				
Male	126	59	126	57
Female	89	41	96	43
WHO performance status				
PS 0	48	22	47	21
PS 1	112	52	119	54
PS 2	55	26	56	25
Stage (Mountain 1997)				
IIIBdry	23	11	20	9
IIIBwet	9	4	14	6
IV	183	85	188	85
Histology				
Squamous cell carcinoma	55	26	45	20
Adenocarcinoma	118	55	131	59
Large cell carcinoma	9	4	12	5
Other/undifferentiated	33	15	34	15
Smoking history				
Never smoker	11	5	15	7
Former smoker	114	53	129	58
Smoker	90	42	77	35

Abbreviations: VC = vinorelbine plus carboplatin; VG = vinorelbine and gemcitabine.

$P = 0.446$; IIIBwet: 7.6 vs 10.8 months, $P = 0.913$; IV: 6.2 vs 6.7 months, $P = 0.924$). Neither did we find any significant association between survival and gender, histology or smoking history (data not shown).

Health-related quality of life

Alive patients completed, VG and VC, respectively, 89% (850 forms) and 90% (910 forms), of the expected HRQoL

questionnaires during the first 17 weeks. The results of pre-specified HRQoL analyses are summarised in Table 2. Vinorelbine plus carboplatin patients had a statistically significantly higher mean score for nausea/vomiting at week 3 ($P = 0.028$) and week 6 ($P = 0.012$), but the difference was only four points. We observed no significant differences between treatment arms after week 17, and neither did other scales or items differ consistently between treatment arms.

Toxicity

Haematological toxicity, adverse events, and hospital admissions are summarised in Table 3. Fewer patients in the VG arm experienced grade 4 neutropenia (VG: 7%; VC: 19%; $P < 0.001$). We found no corresponding difference in the number of patients experiencing febrile neutropenia (VG: 4%; VC: 8%; $P = 0.127$), or other grade 3 or grade 4 infections over all (VG: 20%, VC: 18%; $P = 0.517$). Fewer VG patients experienced grade 3 or grade 4 nausea/vomiting (VG: 4%; VC: 12%; $P = 0.008$). More VC patients received blood transfusions, but the difference was not statistically significant (VG: 10%; VC: 16%; $P = 0.092$).
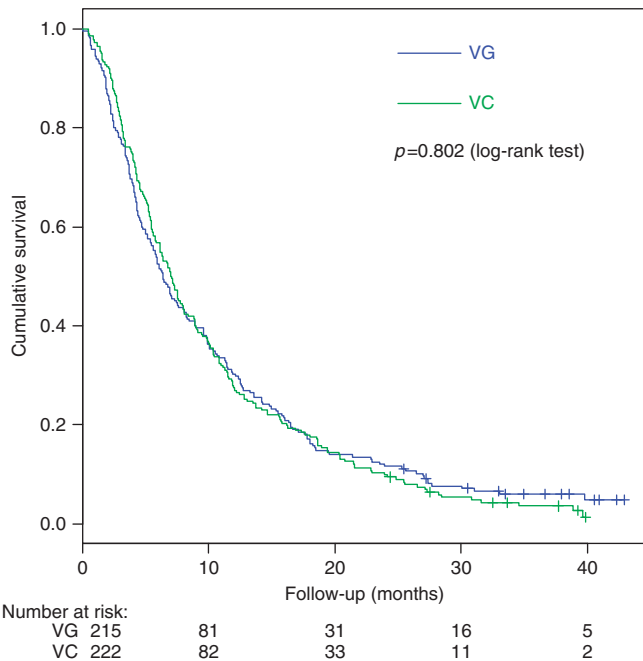
Figure 2 Kaplan–Meier survival plots according to the treatment arms.

Post-study therapy

The use of palliative radiotherapy did not differ between the treatment arms as 101 (47%) VG patients and 111 (50%) VC patients received palliative radiotherapy ($P = 0.497$).

Ninety-one (42%) VG patients and 97 (44%) VC patients received at least one systemic second-line therapy ($P = 0.773$). The most common regimens were erlotinib (25% *vs* 27%), pemetrexed (17% *vs* 15%), and carboplatin-doublets (19% *vs* 9%). The use of systemic second-line therapy was associated with a better PS level (PS 0: 72%; PS 1: 39%; PS 2: 27%; $P < 0.001$) and low age (<75 years: 46%; ⩾75 years: 27%; $P = 0.003$).

DISCUSSION

In this randomised trial we did not observe any difference in overall survival between VG and VC as first-line chemotherapy of advanced NSCLC. Thus, we could not confirm the results from Tan *et al*'s (2005) study where VG was found superior to VC. Our results corroborate a meta-analysis that demonstrated similar survival between carboplatin-based doublets and modern non-platinum doublets (Rajeswaran *et al*, 2008).

During the inclusion period of this study, 1185 individuals in Norway were diagnosed with NSCLC stage IV, whereas the number of stage IIIB patients, specifically, could not be assessed (Norwegian Cancer Registry, personal communication). Hence, the 371 stage IV patients enrolled in this study constituted 31% of these patients nationwide during the period, suggesting this study to be representative for the Norwegian population of patients with advanced NSCLC.

We chose an open-study design to facilitate participation of lung cancer centres of all sizes in this national study. The open design could possibly bias the HRQoL reporting. On the other hand, a blinded study's drawback would be the necessity of a placebo infusion on day 8 in the VC arm, and thereby not reflecting the real clinical practice.

The median survival time was relatively short in both the treatment arms, only 6.3 and 7.0 months for patients in the VG and VC arms, respectively. This survival is lower than the 11.5 and 8.6 months in the study by Tan *et al* (2005). While the median age in their study was 60 years, it was 65 years in ours. They included patients with only Karnofsky PS level of 80–100 points, which approximates WHO PS level 0–1 (Buccheri *et al*, 1996), while we included 25% PS 2 patients. Tan *et al* (2005) did not include patients with brain metastases, which was allowed in the present study. The inclusion of patients with dissimilar important prognostic factors is a plausible explanation for the survival difference between these two studies.

The choice of carboplatin instead of cisplatin is a factor that could have influenced survival negatively in this study. The debate

Table 2 Completion rates of the HRQoL questionnaires and mean scores for the primary HRQoL outcomes

	Baseline		3 weeks		6 weeks		9 weeks		17 weeks		Total	
	VG	**VC**	**VG**	**VC**	**VG**	**VC**	**VG**	**VC**	**VG**	**VC**	**VG**	**VC**
No. of patients alive	215	222	206	219	198	211	184	202	144	165	947	1019
No. of delivered forms	215	222	194	207	169	189	152	161	117	130	847	909
Completion rate (%)	100	100	94	95	85	90	83	80	81	79	89	88
Global QoL	55	55	54	54	54	55	53	55	53	54		
Nausea and vomiting	12	11	12	16*	13	17*	12	15	11	12		
Dyspnoea LC13	38	40	39	40	38	36	37	33	41	37		
Pain C30	31	35	30	33	30	31	31	31	31	32		
Fatigue	47	48	50	50	51	48	49	48	48	47		

Abbreviations: HRQoL = Health-related quality of life; VC = vinorelbine plus carboplatin; VG = vinorelbine and gemcitabine. All scale scores range from 0 to 100. A high global QoL score indicates better QoL, while on the symptom scales, a higher symptom scores indicate more symptoms. *$P < 0.05$; Mann–Whitney *U*-test.

Table 3 Toxicity, transfusions, and adverse events during study treatment period

CTCAE grade	VG n = 213 No. of patients	%	VC n = 221 No. of patients	%	P
Anaemia					0.43
Grade 3	2	1	6	3	
Grade 4	1	0	0	0	
Neutropenia					<0.001
Grade 3	34	16	36	16	
Grade 4	14	7	42	19	
Thrombocytopenia					0.23
Grade 3	6	3	6	2.7	
Grade 4	1	0	3	1	
Transfusions					
Blood	21	10	36	16	0.09
Platelets	1	0	1	0	0.37
Infection					0.52
Grade 3	33	15	31	14	
Grade 4	10	5	8	4	
Febrile neutropenia					0.13
Grade 3	5	2	14	6	
Grade 4	4	2	4	2	
Nausea/vomiting					0.008
Grade 3	8	4	22	10	
Grade 4	0	0	4	2	
Fatigue					0.89
Grade 3	28	13	25	11	
Grade 4	4	2	4	2	
Constipation					0.38
Grade 3	12	6	7	3	
Grade 4	1	0	2	1	
Hospital admissions					
Total	100	48	92	44	0.67
Due to side effects	43	20	52	24	0.87

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; VC = vinorelbine plus carboplatin; VG = vinorelbine and gemcitabine.

on cisplatin *vs* carboplatin is beyond the scope of this paper, but we note that the updated ASCO guideline state carboplatin as an acceptable option in advanced NSCLC, despite a small survival disadvantage (Azzoli *et al*, 2011).

Another question is whether the administration of only three chemotherapy cycles (as compared with four to six cycles recommended in guidelines) has influenced the survival negatively. A Scandinavian study showed that a six-cycle schedule is not significantly better than three cycles (von Plessen *et al*, 2006).

Further, in another Norwegian study from our group, the four-cycle schedule of carboplatin and pemetrexed yielded a similar survival of 7.3 months (Gronberg *et al*, 2009). This suggests that a negative survival contribution from the short treatment length is of only minor significance in this study.

The current study offered combination chemotherapy to both elderly patients and PS 2 patients, while current NSCLC guidelines suggest the use of single-agent therapy in these groups (D'Addario *et al*, 2010). The trend towards a favourable survival of 8.0 months with VC in the elderly patients suggests that this regimen, with a 25% dose reduction, is an acceptable option. However, the poor 4.3 months median survival in PS 2 patients questions the use of toxic and time-consuming combination chemotherapy.

The use of systemic second-line therapy in only 43% of patients may have negatively affected the survival in this study. In selected populations of some clinical trials as many as 67% of the patients received second-line treatment (Ciuleanu *et al*, 2009; Reck *et al*, 2010). In routine clinical practice, however, the rate can be as low as 25% (Ramsey *et al*, 2008). Thus our second-line chemotherapy rate is closer to what is administered in the general clinical routine, presumably a consequence of the representative patient inclusion.

The response rates and survival results of oral vinorelbine are similar to intravenous vinorelbine in advanced NSCLC and breast cancer (Gralla *et al*, 2007; Aapro and Finek, 2011). The advantage of oral vinorelbine is home administration, so that patients, relatives and health care providers can save valuable time. Besides, oral vinorelbine induces no phlebitis, in contrast to the intravenous administration. The disadvantage is more frequent nausea and vomiting, which can be adequately controlled by prophylactic antiemetics. It has been shown that patients prefer taking oral vinorelbine at home instead of intravenous administration at the clinic (Jensen *et al*, 2008). Oral vinorelbine costs more than intravenous vinorelbine, but this is probably outweighed by fewer outpatient visits, quicker and less resource-demanding administration of the drug, and lower transportation expenses (Le *et al*, 2007). Overall, oral vinorelbine can be a useful alternative to the intravenous formulation in advanced NSCLC, especially where the distance to the hospital is substantial.

Both CTCAE reporting and HRQoL measurements indicated slightly more nausea and vomiting in VC patients. The antiemetic regimen differed a little between the treatment groups (VG patients received an i.v. glucocorticoid and 5-HT$_3$-antagonist on day 8, VC patients an oral 5-HT$_3$-antagonist only), but we find it unlikely that this minor difference should explain more nausea and vomiting in VC patients. However, the differences between the treatment arms in HRQoL analyses were below what are considered as clinically relevant, and the difference in grade III/IV adverse events of nausea and vomiting was relatively small. A previous meta-analysis failed to detect any significant difference in nausea and vomiting between non-platinum and carboplatin-based doublets (Rajeswaran *et al*, 2008).

In summary, the current study did not confirm prolonged survival of VG over VC, as first-line treatment in advanced NSCLC. The minor toxicity differences in favour of VG do not justify a change in the treatment practice. Thus, platinum-based doublet chemotherapy remains as the standard first-line treatment.

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