Simplifying Treatment of Advanced Non-small Cell Lung Cancer

Regimen, Route of Administration, and Patients' Preferences

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CONTENT

Summary

Lung cancer is the cancer disease that takes the most lives. Non-small cell lung cancer (NSCLC) is the most common type, and more than half have an incurable disease at the time of diagnosis. Chemotherapy can halt the disease but is only moderately effective, has some side effects and requires regular hospital visits for intravenous infusions. The aim of the current work was to find a more tolerable treatment that is easier to administer and to explore how patients balance the benefits and disadvantages of treatment.

We conducted a national study comparing a chemotherapy combination with fewer side effects (vinorelbine and gemcitabine; VG) with the most commonly used combination in Norway (vinorelbine and carboplatin; VC). Both regimens had a 3-week cycle, with carboplatin given on day 8 and the other drugs on days 1 and 8. The patients went through three cycles. We used vinorelbine in capsule form (oral vinorelbine). This allowed comparison with previous studies in Norway that used intravenous vinorelbine. We also interviewed patients about how large the treatment effect should be to accept treatment.

The VG combination was no better than VC, in terms of overall survival and health related quality of life (HRQoL), and VC remained the preferred regimen for most patients.

Oral vinorelbine had a favourable toxicity profile without compromising survival outcomes. Oral vinorelbine have replaced intravenous vinorelbine on day 8, which allow for home treatment and simplifying the treatment.

Studying patients' attitudes to treatment at the time of diagnosis was complicated. This study suggested that most patients accepted the planned treatment even if the benefits were minimal.

Summary in Norwegian

Forenkling av lungekreftbehandling – pasient- og behandlerperspektiv

Lungekreft er den kreftsykdommen som tar flest liv, både i Norge og globalt. Ikke-småcellet lungekreft er den vanligste typen, og vel halvparten har uhelbredelig sykdom ved diagnosetidspunktet. Cellegift kan bremse sykdommen noe, men har beskjeden effekt, noe bivirkninger, og krever oppmøte på sykehus for intravenøs infusjon. Mindre bivirkninger og enkel gjennomføring av behandlingen er ønskelig. Mer kunnskap om hvordan pasientene balanserer nytte og ulemper er også ønskelig.

Vi gjennomførte en nasjonal studie som sammenliknet en cellegiftkombinasjon med noe mindre bivirkninger, vinorelbin-gemcitabin (VG), med den etablerte kombinasjonen vinorelbin-karboplatin (VC). Vi brukte vinorelbin i tablettform (oral vinorelbin), slik at vi kunne sammenlikne resultatene med tidligere studier i Norge, der medisinen ble gitt intravenøst.

Hovedfunnene er at VC var minst like bra som VG, og brukes derfor fortsatt. Oral vinorelbin viste seg like bra som intravenøs, og har forenklet behandlingen.

Pasientens vurderinger er utfordrende å undersøke på diagnosetidspunktet, som er preget av krise og fokus på behandling. Undersøkelsen antyder at pasientene vil takke ja til planlagt behandling også når nytten er minimal.

Scientific Environment—the Context of This Work

My Clinical Practice

Lung cancer has been the main topic of my clinical work at Haukeland University Hospital, Department of Thoracic Medicine, since I started working there in 2001. Researching and improving care has always been central to our work and encouraged by the leader team.

The Norwegian Lung Cancer Study Group

Since 2000, the Norwegian Lung Cancer Study Group (NLCG) has designed and carried out several clinical lung cancer studies. These studies have been integrated into routine clinical practice and directly influenced clinical practice in nearly all departments treating patients with lung cancer. The NLCG board also participated in writing the protocol for this study. All physicians in Norway interested in lung cancer may join the NLCG. I have contributed actively to the NLCG's work since 2005.

Implementation of research results is essential so that the patients can benefit from the results. In this realm, an important activity of the NLCG is developing national guidelines on the treatment of lung cancer.

Acknowledgements

Clinical research on lung cancer requires that many people work jointly. Consequently, as a researcher with some clinical background in the area of interest, I have been dependent on a workplace and a network to conduct the research within. I will thank in person a few of them who have supported me.

My first thanks are due to the Department of Thoracic Medicine at Haukeland University Hospital, headed by Kahtan Al-Azawy most of the time during my PhD education period. Kahtan has fully supported my work, including showing genuine interest in the project.

Christian von Plessen has been my patient main supervisor for many years. We planned the study together, and we were both responsible for the conducting of the study. His intellectual insight and support, and linguistic skills, have all been highly appreciated.

Ernst Omenaas was my long-time co-supervisor, and assisted with his experience over his long academic career until his retirement. He gave much important advice along the way and contributed valuable comments on manuscripts. Marianne Aanerud have co-supervised me for the last year and inspired me to finish my work. I owe great thanks to both of you.

The NLCG, headed by Stein Sundstrøm when the VG study started, contributed to both planning and conducting the study. My thanks also go to the NLCG co-authors, particularly Bjørn Henning Grønberg for his always valuable discussions and rapid responses to manuscripts. Of the utmost importance was the tremendous work done by the investigators and nurses at 35 Norwegian hospitals who recruited patients and collected data.

I want to thank the Centre for Shared Decision Making and Collaborative Care Research at Oslo University Hospital, represented by Cornelia Ruland and Fredrik Svensen, for their scientific and technical support to the project.

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Approvals

The Regional Ethic Committee for Medical and Health Research ethics approved the study.

The Norwegian Social Science Data Service (*Norsk Samfunnsvitenskapelige Datatjeneste*) acted as the data protection officer and recommended the study.

The Norwegian Medicines Agency (*Statens Legemiddelverk*) approved the study.

The Drug Liability Association (*Legemiddelansvarsforeningen*) carried liability insurance for clinical trials of drugs.

We registered the trial at Clinicaltrials.gov, identifier: NCT00737867.

The National Insurance Administration (*Rikstrygdeverket*) approved use of oral vinorelbine with reimbursable prescriptions (*blåresept-ordningen*).

Abbreviations

ALK translocation: anaplastic lymphoma kinase translocation; a fusion gene defect in the gene coding for anaplastic lymphoma kinase

AUC: area under curve; related to the dosing of carboplatin in this dissertation

CT: chemotherapy

CTCAE: common terminology criteria for adverse events

EGFR: epithelial growth factor receptor

EORTC: European Organization for Research and Treatment of Cancer

HRQoL: health-related quality of life

KM: Kaplan-Meier

NLCG: Norwegian Lung Cancer Study Group

NSCLC: non-small cell lung cancer

OS: overall survival.

PD-1: programmed cell death protein 1

PD-L1: programmed cell death-ligand 1

PFS: progression-free survival, defined as the length of time from randomisation until death or progression of the disease

PC: palliative care

PS: performance status in which 0 is asymptomatic, and 5 is death

ROS1: c-ros oncogene 1

VC: vinorelbine and carboplatin

VG study: acronym for the main study: Vinorelbine and gemcitabine versus vinorelbine and carboplatin in advanced non-small cell lung cancer

List of Publications

[1] O. Flotten, B.H. Gronberg, R. Bremnes, T. Amundsen, S. Sundstrom, H. Rolke, K. Hornslien, T. Wentzel-Larsen, U. Aasebo, C. von Plessen, 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, Br. J. Cancer, 107 (2012) 442–447.

[2] O. Flotten, B.H. Gronberg, S. Sundstrom, N. Helbekkmo, R. Bremnes, C. von Plessen, Oral versus intravenous vinorelbine in advanced NSCLC—a retrospective comparison, Cancer Treatment and Research Communications, 9 (2016) 15–20.

[3] O. Flotten, M. Aanerud, C. von Plessen, Informed patients with newly diagnosed advanced NSCLC accept chemotherapy for little or nil benefit, submission in process (2019).

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Introduction

Lung cancer is the most common cause of cancer death. Most patients with lung cancer, 85%, have non-small cell lung cancer (NSCLC) histology. Adenocarcinoma, squamous cell carcinoma and large cell carcinoma are the most common subtypes. At the time of diagnosis, most patients have an advanced, metastatic or non-curable disease [1]. *Advanced*, *metastatic* and *non-curable disease* are overlapping terms. In this thesis, I prefer to use the term advanced *NSCLC*, meaning that the disease is not amenable to local treatment (radiation or surgery) with a curative intention. The expected lifespan is short as most patients die within a year after diagnosis.

The Role of Chemotherapy in Advanced Non-Small Cell Lung Cancer

The scientific basis for the use of chemotherapy in advanced NSCLC was established in 1995, when a meta-analysis showed a modest effect, with an increase in median survival from 4.5 to 6 months [2]. The standard treatment is to offer 3–6 courses in 3-week cycles with a platinum doublet, commonly either carboplatin or cisplatin combined with a so-called third-generation cytotoxic drug, such as vinorelbine, gemcitabine, paclitaxel and pemetrexed [1]. The benefits from cytotoxic chemotherapy are modest, and side effects such as nausea and immunosuppression are common.

Second-Line Chemotherapy

After receiving chemotherapy, all patients with advanced NSCLC sooner or later experience disease progression and eventually die. Some experience disease progression while on treatment, indicating no benefits whatsoever from the treatment, while others experience disease progression at some point in time after discontinuation of treatment. *Second-line treatment* refers systemic treatment after termination of first-line treatment. The established options for second-line treatment are docetaxel [3], erlotinib [4] and, for those with non-squamous histology,

pemetrexed [5]. Another option for patients who have responded to treatment is a re-challenge with the given first-line treatment regimen.

Pemetrexed Maintenance Chemotherapy

Maintenance chemotherapy with pemetrexed as an extension of first-line treatment can prolong survival in the subgroup of patients with the adenocarcinoma subtype [6, 7]. However, this treatment does not apply to all patients. Paramount et al. recruited patients before the start of first-line treatment and randomised them to pemetrexed maintenance treatment, or placebo, after completion of first-line treatment. Only 57% were eligible for randomisation [6]. Similar result was found in a Norwegian trial that studied late (second-line) vs immediate (maintenance) pemetrexed in advanced non-squamous NSCLC. In this study, the patients were also recruited before starting their first-line treatment, and after first-line treatment, only 45% were eligible for randomisation between maintenance treatment and observation (currently unpublished data, personal communication, Clinicaltrials.gov NCT02004184). These findings indicate that maintenance treatment with pemetrexed is not applicable for many patients with advanced NSCLC.

PD-1/PD-L1 Axis Inhibitors—Immunotherapy

The results from several phase III trials have confirmed the effectiveness of drugs targeting the PD-1/PD-L1 axis (programmed cell death-1 and its ligand PD-L1). Such treatment is commonly called *immunotherapy*. Guidelines recommend a treatment course for most patients with advanced NSCLC at some point in time [8]. High PD-L1 expression in tumour cells is correlated with high response rates but does not precisely distinguish between responders and non-responders. Recent studies have shown that adding pembrolizumab, a PD-1 inhibitor, to a platinum combination in first-line treatment prolongs the survival of NSCLC patients with adenocarcinoma [9] and squamous cell carcinoma [10]. Currently, the price of pembrolizumab is an obstacle to its use in combination with chemotherapy in Norway. Patients with high (>50%) PD-L1 expression in tumours receive pembrolizumab as first-line

monotherapy, while other patients with at least 1% PD-L1 expression receive a PD-1/PD-L1 inhibitor, in accordance with current prices, as second line treatment.

Bevacizumab

Adding bevacizumab to platinum-based chemotherapy in selected patients prolongs progression-free survival (PFS). The E4599 trial also showed an overall survival (OS) benefit; however, it was limited to men [11]. The AVAIL trial confirmed a PFS benefit but detected no prolongation of OS [12]. Use of bevacizumab in Norway is limited.

Drugs Targeting ALK/EGFR/ROS1 Alterations

Patients with tumours harbouring anaplastic lymphoma kinase (ALK) translocation, epithelial growth factor receptor (EGFR) mutation or c-ros oncogene 1 (ROS1) mutation benefit from treatment with a specific tyrosine kinase inhibitor [8]. Such treatment applies only to a minority of patients with advanced NSCLC, approximately 10%–15%.

Patients' Treatment Preferences

Evaluation of treatment requires assessing and measuring one or several endpoints. This thesis intends focus on endpoints relevant to patients. Poor prognosis is prominent in advanced NSCLC. Most patients consider life extension to be their most important treatment goal, with health-related quality of life (HRQoL) and avoidance of side effects relevant secondary goals [13].

Life extension means improving OS, which is the time from diagnosis or randomisation in clinical trials until death. Survival is also an easily assessed measure to monitor the situation in routine clinical practice. In Norway, the Norwegian Cancer registry reports the survival of lung cancer patients.

Several validated instruments are commonly used in cancer trials to assess the endpoint of HRQoL, a patient-reported outcome. Measuring HRQoL adds

information about the benefits and toxicity of treatment, and HRQoL scores are also correlated with prognosis [14, 15]. However, a generally accepted standard of what changes and differences in scores are clinically important is lacking [16].

Rationale for the Studies

Platinum vs No-Platinum Combination Chemotherapy

As described, platinum-based doublet chemotherapy is the standard first-line treatment for most patients with advanced NSCLC, optionally combined with pembrolizumab, if available at lower prices.

Some studies have suggested the use of non-platinum combinations. For instance, Tan et al. found that the combination of vinorelbine and gemcitabine (VG), which is less toxic than with the combination of carboplatin and vinorelbine (VC), yields an additional 3 months of survival in advanced NSCLC [17]. We found this difference surprising, and given that the VC combination is the most commonly used first-line treatment for advanced NSCLC in Norway, conformation of the results of Tan et al. could promote replacing the VC combination with the less toxic VG combination.

Oral vinorelbine

Patients treated with the VC combination receive vinorelbine on days 1 and 8 and carboplatin on day 1. Vinorelbine is also available in an oral formulation, which allows for home treatment on day 8, saving time for patients and health professionals. The use of oral vinorelbine in advanced NSCLC has been outlined and includes treatment as a single-agent treatment in with combination chemotherapy and as maintenance chemotherapy instead of pemetrexed [18]. Importantly, patients prefer the oral vinorelbine formulation [19]. Although the oral vinorelbine formulation is an attractive option, data from large, phase III trials are lacking. Using oral vinorelbine in a large trial, therefore, could add valuable information about its characteristics.

Patients' View on Chemotherapy

Unfortunately, the benefits from platinum doublet chemotherapy in advanced NSCLC are modest, and side effects are common. Treatment decisions in this situation are

complex. Patients' lack of understanding of their own situation raises concerns that the decisions may not be shared but, rather, physician controlled [20-23]. Surprisingly, no studies have yet been published on how chemotherapy-naïve patients with advanced NSCLC view the balance between effect and side effects. If we better understood how patients decide their treatment, we might be able to improve the communication and decision process in this situation.

Objectives

The general aim of this thesis is to simplify treatment for patients with advanced NSCLC without compromising the effectiveness. I want to better understand how patients balance the benefits and side effects. This goal translates into three questions in this thesis:

1. Can we omit platinum drugs in advanced NSCLC?
2. Are the outcomes of oral and intravenous vinorelbine similar?
3. How do chemotherapy-naïve patients with advanced NSCLC weigh the benefits and side effects?
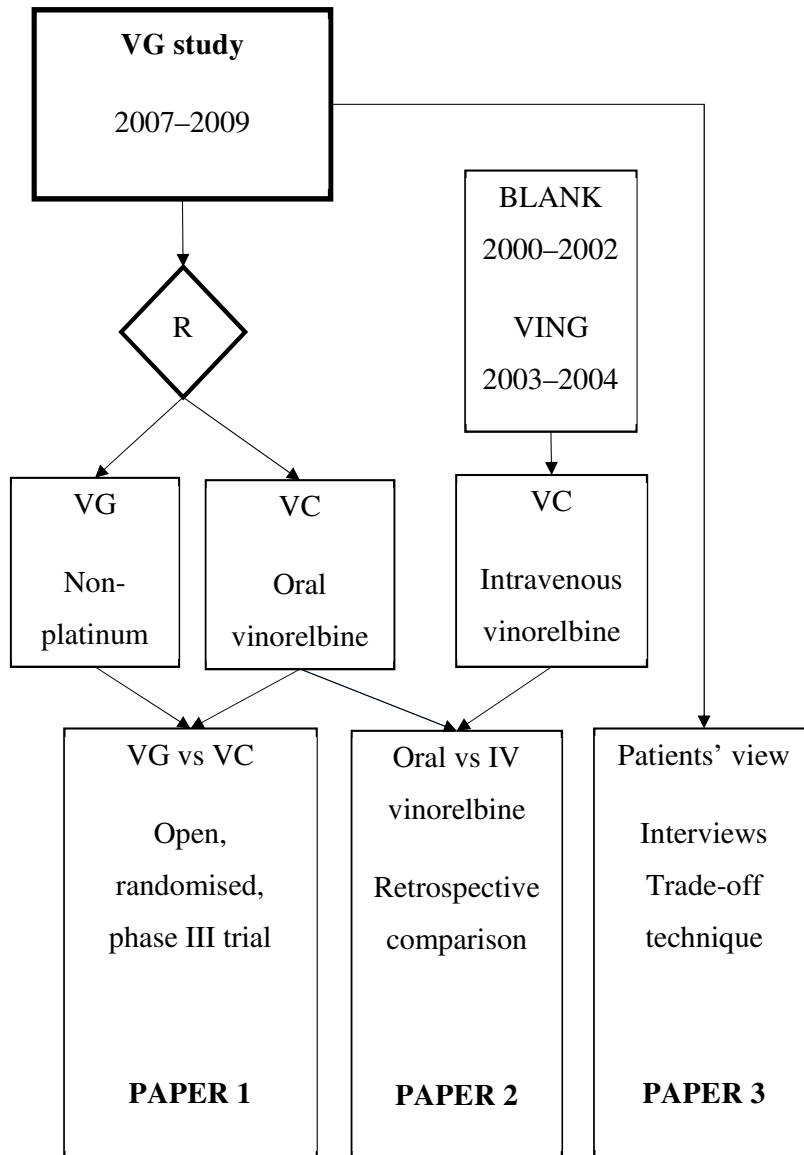
Figure 1. Overview of the patients and papers in the present work. VG = vinorelbine and gemcitabine, VC = vinorelbine and carboplatin, IV = intravenous, R = randomisation, VING/BLANK = two previous chemotherapy trials using vinorelbine and carboplatin.

Methods and Subjects

Study Centres, Patients and Design

The VG study, which we conducted, was an open, randomised, phase III study. Physicians at 35 Norwegian hospitals recruited and treated patients as part of their routine practice, so a referral to a study centre was not necessary. For the comparison of oral and intravenous vinorelbine, we utilised also data from two earlier advanced NSCLC trials (Figure 1).

Eligible patients in the VG study had NSCLC stage IIIB or stage IV following Mountain's classification (1997; [24] and were not amenable to treatment with curative intent. The patients had not previously received chemotherapy for lung cancer and underwent a computed tomography scan before enrolment. They had performance status (PS) 0–2. Bowel disease affecting absorption of oral vinorelbine was an exclusion criterion.

Randomisation

Before randomisation, the patients completed the baseline HRQoL form. The physicians contacted a central study centre at Haukeland University Hospital (Kontor for Klinisk Kreftforskning; KKK) by phone for stratified block randomisation. The strata were:

1. PS 0–1 vs PS 2
2. Stage IIIB vs stage IV
3. Age < 75 years vs ≥ 75 years

Treatment

The treatment schedule resembled that in routine clinical practice, with 3-week cycles.

VG

- o Day 1: Vinorelbine capsules 60 mg/m^2 and gemcitabine infusion 1000 mg/m^2
- o Day 8: Vinorelbine capsules 60 mg/m^2 and gemcitabine infusion 1000 mg/m^2
- o Day 22: Cycle no 2
- o Day 43: Cycle no 3

Gemcitabine and vinorelbine were dosed according to body surface area following Dubois and Dubois's formula [25].

Regarding gemcitabine and radiation, we required at least 3 days from gemcitabine to radiation and at least 2 weeks from radiation to gemcitabine.

VC

- o Day 1: Vinorelbine capsules 60 mg/m^2 and Carboplatin (AUC 5)
- o Day 8: Vinorelbine capsules 60 mg/m^2
- o Day 22: Cycle no 2
- o Day 43: Cycle no 3

We used Calvert's formula for carboplatin dosing [26] and Cockcroft-Gault's formula to estimate the glomerular filtration rate [27].

Dose Adjustments

The protocol-specified dose adjustments or reasons for delaying a dose were:

- o Patients ≥ 75 years, who received 75% of the full dose
- o Neutropenia or thrombocytopenia
- o Neutropenic infections
- o Other toxicity at the physician's discretion

Endpoints and Power Calculations

OS was the primary endpoint, and the study had, presumed 444 randomised patients, 80% power to detect an increase in 1-year survival from 29%, as observed in our previous studies, to 40%, with a 5% significance level.

HRQoL was a secondary endpoint. As in previous NLCG trials, we used the European Organization for Research and Treatment of Cancer (EORTC) QlQ-C30 form and LC13 module for this purpose [28]. The questionnaires are shown in Appendix.

The QlQ-C30 measure symptoms commonly reported by cancer patients, while the LC13 module measure symptoms associated with lung cancer.

The QlQ-C30 have in total 15 scales, nine are multi-item, and six are single-item scales (table 1). The LC13 module have 13 questions and measures symptoms commonly associated with lung cancer and its treatment.

When answering the QLQs, the patients give a score from 1-7 for the two questions about global QoL, and from 1-4 on the other questions.

We pre-specified the following HRQoL analyses: differences between the treatment arms in global quality of life and symptom scales for pain, nausea/vomiting, dyspnoea and fatigue. The dimension global quality of life at week 9 was the main HRQoL endpoint. We calculated that 70 patients in each treatment arm would be sufficient to detect differences in mean scores of 11 points or more on scales of 0–100, with 80% power and 5% significance level. Thus, with 222 patients in each arm, the study had the power to detect relevant HRQoL differences.

Other secondary endpoints were haematological toxicity and the need for palliative radiotherapy.

Assessments and Follow-up

The patients completed the first HRQoL form before randomisation, every third week during treatment (0, 3, 6 and 9 weeks) and every eighth week after treatment (e.g. 17 and 25 weeks).

Blood tests were performed weekly during treatment in the local hospitals' laboratories in accordance with local standards and routines.

We performed no formal response evaluation. Detection of disease progression and decisions about second-line treatment were left to local physicians and local routines.

Table 1 Content of the EORTC QLQ-C30 and LC13 questionnaires

QLQ	Type of scale	Scale	No. of items	Question no.
C30	**Global health**	Global QoL	2	29,30
	Functional scales	Physical function	5	1-5
		Role function	2	6,7
		Emotional function	4	21-24
		Cognitive function	2	20,25
		Social function	2	26,27
	Symptom scales	Fatigue	3	10,12,18
		Nausea, vomiting	2	14,15
		Pain	2	9,19
		Dyspnoea	1	8
		Insomnia	1	11
		Appetite loss	1	13
		Constipation	1	16
		Diarrhoea	1	17
		Financial difficulties	1	28
LC13	**Symptom scales**	Dyspnoea	3	3-5
		Coughing	1	1
		Haemoptysis	1	2
		Sore mouth	1	6
		Dysphagia	1	7
		Periph. neuropathy	1	8
		Alopecia	1	9
		Pain in chest	1	10
		Pain arm or shoulder	1	11
		Pain in other parts	1	12

The LC13 module also has two questions about the use of pain killers, see appendix.

Data collection on adverse events focused on nausea/vomiting, fatigue, constipation, infections, neutropenic fever, blood transfusions and hospitalisations. For each chemotherapy cycle, the treating physician completed a form on the treatment administered, PS, weight and blood tests.

The central study office, KKK, collected all the data, kept the trial database updated and sent reminders to clinicians. For each chemotherapy course, the KKK also sent the HRQoL forms directly to the patients to be returned to the office. If the forms were not returned, the KKK sent one reminder.

Analyses

OS analyses followed the intention to treat principle. A Kaplan Meier (KM) plot, log-rank test and multivariate Cox regression were used.

We calculated the scores for HRQoL according to the scoring manual [29]. The raw scores were transformed to a scale from 0-100. A high score on functional scales means a good function or quality, while a high score on symptom scales means severe symptoms. If more than half of the items in a scale were missing, the scale score was defined as missing. We calculated mean scores for every time point and tested group differences with the Mann-Whitney U test.

Toxicity analyses included only the patients receiving at least one treatment cycle, and group differences were tested with the Mann-Whitney U test.

For categorical variables, we used the Chi-square test.

Comparison of Oral with Intravenous Vinorelbine

Oral and intravenous vinorelbine were compared in a retrospective study on three study cohorts of patients receiving VC. We pooled data from the VG study (paper 1 of this thesis) with data from two earlier NLCG trials [30, 31]. The results for the patients on oral vinorelbine in the VG study's VC arm were compared with historic results from VC patients on intravenous vinorelbine. The three trials had very similar inclusion criteria, used the same instruments and intervals for assessment of HRQoL and measured haematological blood tests at the same intervals and time points. The main difference was the formulas used for dosing carboplatin. Chatelut's formula with area under the curve (AUC) 4 was used in the two trials with intravenous vinorelbine, while Calvert's formula AUC 5 was used in the VG study with oral vinorelbine. We compared OS in a KM plot, using the log rank-test and multivariate Cox regression with second-line treatment as a time-varying covariate.

Haematological toxicity was categorised according to the common terminology criteria for adverse events (CTCAE) catalogue, and group differences were tested with the Chi-square test. HRQoL was presented with mean scores and mean change scores, and we tested group differences with the t-test.

Patients' Preferences for Chemotherapy

The aim of this interview-based study was to explore at what benefit threshold patients would chose chemotherapy. We collected data through structured interviews using trade-off techniques.

This research was performed as a sub-study of the VG study at five selected centres. The patients were first allocated to their respective treatment regimens in the VG study. A trained nurse or physician interviewed the patients on day 1 of the first chemotherapy cycle before chemotherapy administration, and on day of the third cycle.

The interviewer used an interactive touchscreen to present information and perform the interviews. The questionnaire utilised the time and the probability trade-off

techniques [32]. The patients were asked to choose between palliative care (PC) and chemotherapy based on the initial assumption that these options could provide equal, expected survival outcomes. If the patients chose PC, the expected difference in the outcomes of chemotherapy and PC increased in favour of CT until the patients switched to CT. This switch indicated the preference threshold for accepting chemotherapy.

The preference threshold for chemotherapy was elicited in four scenarios, two exploring thresholds with expected survival expressed in months and two with thresholds expressed as the probability of being alive at 12 months.

For analyses and result presentation, we used descriptive statistics and graphical displays of individual responses.

Summary of Papers

First Paper: Non-Platinum Combination in Advanced NSCLC

Objective: We conducted a national, randomised study to compare a non-platinum combination and a platinum combination in advanced NSCLC first-line treatment.

The endpoints were OS, HRQoL, toxicity and use of palliative 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 OS was 6.3 months for VG and 7.0 months for VC (P 0.802). VC 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 use of radiotherapy did not differ significantly among the treatment groups.

Conclusion: The two regimens yielded similar OS. The VG combination had only a slightly better toxicity profile. The VG study did not undermine the role of a platinum combination as the standard first-line treatment for advanced NSCLC.

Second Paper: Oral Vinorelbine in Advanced NSCLC

Objective: We compared outcomes of oral and intravenous vinorelbine, both combined with carboplatin as first-line treatment for advanced NSCLC, using data from three chemotherapy trials. The end points were OS, HRQoL and haematological toxicity.

Results: A total of 222 and 368 patients received oral or intravenous vinorelbine, respectively. The OS (median 7.0 vs. 6.9 months), chemotherapy compliance, HRQoL outcomes and toxicity were similar, although oral patients reported less worsening of constipation and had fewer adverse events of grade III–IV leukopenia and anaemia.

Conclusion: Oral 60 mg/m² vinorelbine and intravenous 25 mg/m² provided similar survival outcomes. The HRQoL outcomes were similar or favoured oral vinorelbine. Oral vinorelbine caused less haematological toxicity. The results support the use of oral vinorelbine on day 8 in treatment with VC for advanced NSCLC.

Third Paper: Patients' Preferences for Chemotherapy

Objective: We interviewed chemotherapy naïve patients with advanced NSCLC to assess, in terms of life extension, what benefit they would require to accept treatment. The study applied both the time trade-off and the probability trade-off techniques.

Findings: We performed 54 interviews with 30 patients. Half of the patients indicated that they required nil benefits to choose chemotherapy. The subjects made negligible changes to their answers between the baseline and the interviews after 6 weeks. The patients and investigators gave anecdotal reports of the difficulties concerning the clarity and severity of the prognostic information supplied in the questionnaire.

Conclusion: The majority of the patients would accept chemotherapy for nil or very marginal benefits before and after treatment. The topic of patients' attitudes towards toxic chemotherapy is complex, and future studies should focus on these decision processes later in the disease course.

Discussion of Methods

Study Setting, Design and Implementation

The embedding of lung cancer trials in clinical routine practice worked well in Norway previously, and together with the wide inclusion criteria, it ensured a low threshold for patients with advanced NSCLC to enter the VG study.

A randomised design is the standard method for excluding systematic errors in medical research aiming at comparing efficacy of two treatment regimens. The use of stratification avoided an imbalance of certain prognostic factors (strata) in the two treatment groups [33]. Randomisation at the central study office eliminated bias in the allocation of treatment.

The open design was more feasible and far less costly than a placebo-controlled design. Blinding and a placebo-controlled design have been considered to be relevant when using any subjective outcome measures [33]. For the primary endpoint of OS, this is not a major concern. Knowledge about treatment regimens could have theoretically biased the HRQoL measures. However, a placebo-controlled design would have also required hospital visits for all medications, which would have precluded home treatment on day 8 in the VC arm. Consequently, the study would not have reflected real-life situations. The design soundly balances the trade-off between the optimal exclusion of bias and representativeness of real-life situations.

For comparison of oral and intravenous vinorelbine, the retrospective, non-randomised design introduced some risk of bias. The study setting and the inclusion criteria were similar across the trials, but a competing trial recruited stage IIIB patients at the same time as the VG study, affecting the proportion of stage IIIB patients [34]. This situation potentially could have introduced a risk that the two groups compared had different prognoses, thereby biasing the comparison of interest. The retrospective design also introduced a risk that unknown confounding factors might bias the comparison.

Treatment

Several formulas for carboplatin dosing exist, and most account for renal function [27, 35]. Measuring the creatinine clearance with radionuclide methods is difficult in everyday oncology practice, and using serum creatinine level for calculating renal function is regarded acceptable. Calvert's formula is one the commonly used formulas for this purpose [36]. The carboplatin dosing with Calvert's formula and AUC 5 corresponds to Chatelut's formula with AUC 4, which was used with intravenous vinorelbine in the two trials, but entails a higher carboplatin dose in women and a lower dose in men (author's calculations). This difference in carboplatin dosing introduces a potential bias towards more leukopenia and anaemia in women on oral vinorelbine and justifies subgroup analyses to explore toxicity related to the two formulations.

The 60 mg/m^2 dosing of oral vinorelbine correspond to the intravenous 25 mg/m^2 dose [37], which we used in previous trials [30, 31]. The gemcitabine dosing was in line with practice in combination chemotherapy [17, 31].

The 25% dose reduction in elderly patients ≥ 75 years old has been standard practice in both trials and clinical practice in Norway. Its scientific foundation can be questioned, though, as Calvert's formula already accounts for age [38]. Overall, the treatment procedures in the studies were in line with clinical routine practice and did not complicate participation in the trial.

End Points

OS and HRQoL reflect what the patients regard as the most important attributes of therapy [39]. OS is considered to be an easily and precisely measured and reliable end point in clinical trial, based on objective assessments. A limitation of OS as an endpoint is that it is influenced not only by the study treatment but also by any treatment administered after the study treatment (second-line treatment).

An alternative to OS, progression-free survival (PFS), is a composite endpoint used in many clinical oncology trials today and is commonly reported as the primary

endpoint. PFS is a reasonable endpoint if treatment after the study treatment substantially affects OS. Second-line treatments are increasingly used. In this project, PFS could have added valuable information, especially in the comparison of oral and intravenous vinorelbine. However, regularly response assessment with computer tomography after treatment was not a standard procedure at the time of the VG study and would have added substantial costs to the study.

The EORTC QLQ-C30 and LC 13 questionnaires have been used in several lung cancer trials in Norway. Delivering the HRQoL forms by mail to the participants has worked well previously and ensured standardised instructions to all the participants. The validity and reliability of these instruments has been reported elsewhere [40], and we regarded these instruments as good indicators of the patients' situation during and shortly after the treatment period. However, the wording of the questionnaire items directed the respondents' attention to experiences during the preceding week, not the entire 3-week chemotherapy cycle. The timing and number of assessments could influence the likelihood of detecting differences in HRQoL during chemotherapy, and day 4 in the chemotherapy cycle has been proposed as the best time point for assessing alterations in HRQoL [41]. Delivering the forms every third week was a compromise between the patients' workload and the additional information gained at the risk that transient substantial side effects would go undetected.

The HRQoL information gathered after the treatment period probably had little value, and the information gathered after 17 weeks, in particular, probably added no substantial information about the situation during the chemotherapy period.

In the toxicity comparison in paper 2, only haematological toxicity was compared as data on other adverse events (AE) were not collected uniformly across the three trials. Bioavailability studies could have been valuable to highlight the comparison of formulations but were beyond the scope of the VG study.

Patients' Perspectives

The lack of research standards in this field is challenging, and the contextual situation could influenced bias in the answers. The patients had already decided to receive

chemotherapy in the chemotherapy trial. We did not assess their knowledge about their situation or systematically inform them about their prognosis before the interviews. The patients' lack of familiarity with the situation was also obvious. A strength of the study was the performance of two interviews, which enabled observing whether the responses changed during treatment. The study design was exploratory, which the interpretation of the findings needed to reflect.

Statistical Analyses

The survival analyses followed the intention to treat principle with standard test methods. Sub-group analyses were relevant for age groups < 75 and ≥ 75 years, according to the practice of dose reduction in the elderly. For comparison of oral and intravenous vinorelbine, multivariate Cox regression analysis was helpful to adjust for confounders. Adjustment for the use of second-line treatment, a time-varying covariate, is problematic as use of second-line treatment is itself a marker of worsening of the disease. However, assuming equal distribution of disease progression in the two arms, the use of this time-dependent covariate adjusted for differences in the use of second-line treatment.

Regarding the HRQoL analyses, analyses of mean scores and mean changes since baseline have been criticised [42] as they risk not detecting small differences. Time to deterioration, area under the curve, and linear mixed models for longitudinal data have been proposed methods. Osoba et.al have advocated for a simpler approach, including analyses of mean scores and mean changes [43]. We also used different test methods (Mann Whitney U test and t-test) in paper 1 and paper 2. In general, agreement on and standardisations of how to analyse and present HRQoL analyses in clinical cancer trials are lacking. More importantly, our study samples were sufficiently large to detect the predefined clinically relevant group differences of 11 points.

Regarding haematological toxicity, the use of data only from patients who had received at least one chemotherapy course seems to have been appropriate. The use of different test methods (the Mann-Whitney U test in paper 1, and the categorisation of

the CTCAE catalogue and Chi-square test in paper 2) probably have minor importance.

Reliability

Reliability refers to the consistency of a measure, or the reproducibility of a measurement when repeated at random in the same subject or specimen [44]. Time of death and OS are probably not subject to systematic bias, and if most subjects are observed until death (few censures); OS will also be a highly reliable measure of survival in the sample.

For the HRQoL end point, the reliability of the EORTC QlQ-C30 and LC13 module has been confirmed, with the exception of the dimension of cognitive functioning [40]. Regarding haematological toxicity, we assumed that the laboratories at the local hospitals provided services of satisfactory quality and reliability for the purpose of this study and in line with the accepted standards.

In the study on the patients' perspectives, the reliability of this test procedure has not been evaluated in the actual context.

Internal Validity

Internal validity concerns the conclusions within the study context and means that the observed differences between groups are related to the intervention tested [45]. The high internal validity of the randomised VG study was indicated by the randomised design, relevant statistical analyses, use of relevant, reliable, predefined endpoints, adequate powering of study and the process to ensure the completeness of the data.

Regarding the HRQoL measures, the sample size was larger than needed to detect clinically meaningful differences. Data attrition, which is inevitably in advanced cancer trials, however, can threaten the validity. If the survival or the complication rates are different at a time point when HRQoL assessment, this will complicate the interpretation of HRQoL analyses.

Regarding the comparison of oral and intravenous vinorelbine, the retrospective, non-randomised design is a relevant weakness and has the potential to bias the analyses and thereby affect internal validity. The statistical methods cannot fully account for this possibility, so interpretation of the results must take into account these challenges.

Regarding the patients' perspectives, the internal validity of paper 3 is difficult to evaluate due to the lack of standardisation of research methods in this research field.

External Validity

External validity refers to the usefulness of results outside the study context. The result must be relevant outside the trial to the group they are supposed to represent, and the end points must be clinically relevant [46]. The study setting, wide selection criteria, relevant endpoints and representation of an everyday routine practice are were relevant to clinical routine practice and are indicators of external validity. Regarding paper 3, however, one should keep in mind that the interview situation differed significantly from routine practice, and the arguments for external validity are questionable.

Discussion of the Main Results

Main Findings

The VG study, a randomised, phase III trial conducted in routine lung oncology practice in Norway, did not confirm the superiority of VG over VC for patients with advanced NSCLC (paper 1).

In the study, oral vinorelbine was administered, and the comparison with intravenous vinorelbine, used in two previous trials, indicated that oral vinorelbine yielded similar OS and HRQoL outcomes. Some HRQoL scales and haematology analyses indicated less toxicity than the oral formulation (paper 2).

In a subset of the patients, interviewed before start of treatment about their preferences, most of them would accept to receive chemotherapy for a very low or nil benefit threshold (paper 3).

The strength of the VG study relates to being conducted in routine clinical practice, as were also our previous trials [47, 48]. The accrual time of the VG study was a little longer, 19 months instead of 15 months. The difference partly results from inclusion of a smaller proportion of stage IIIB patients due to a competing trial [34]. We estimated that 31% of Norwegian patients with stage IV NSCLC entered the trial during the recruitment period. The VG study thus recruited a large proportion of the patient population, and hopefully, this large proportion was representative of that population.

The median survival of 7 months and the hospitalisation of 44% of the patients during the treatment period reflects the poor prognosis and high disease burden in this patient group.

Our findings of similar OS for VC and VG differed from Tan et al., who reported a superior OS of 11.5 months in the VG arm compared to 8.6 months with VC [17]. Some differences in the study design are notable. We included older patients (median 65 years old vs 60 years old) and allowed inclusion of patients with PS 2 and brain metastases. We administered a fixed treatment regimen of three cycles. Tan et.al

administered up to six cycles depending on the response. They also administered a higher vinorelbine dose of 30 mg/m^2 in the VC arm. None of these differences, though, can explain that we could not confirm the superiority of VG over VC. However, our practice of dose reduction in the elderly lacks scientific support, and the finding (post-hoc analyses) of the elderly patients in the VG arm who had inferior OS with VG could indicate less than optimal drug exposure in elderly VG patients.

The HRQoL results in both papers 1 and 2 should be interpreted cautiously. We observed a decline in the questionnaire completion rate from 100% at baseline to 80% at weeks, indicating modest data attrition. In the randomised VG study, the detected differences in the groups' HRQoL scores were small, far less than the pre-defined threshold of 11 points. The completion rates of the two groups were similar, making it less likely that a significant difference was not detected, although it cannot be ruled out [49].

In the comparison of oral and intravenous vinorelbine in paper 2, one should also take into account that multiple scales were tested, which increased the risk of, by chance, observing differences that were not true. The differences in the scales constipation (during treatment), peripheral neuropathy and alopecia, however, consistently favoured oral vinorelbine. A reasonable interpretation is that it supports that oral vinorelbine 60 mg/m^2 is less toxic than intravenous 25 mg/m^{2,}, as shown in the analyses of haematological toxicity.

A plausible explanation for the lesser toxicity of oral vinorelbine is the lower and slower achievement of a peak concentration of vinorelbine [50, 51]. Another possible explanation is that the assumption of similar drug exposure with oral 60/m^2 and IV 25/m^2 is not entirely true. Bias from different carboplatin dosing is not a likely explanation as women with higher carboplatin doses under Calvert's formula with AUC 5 had less haematological toxicity than with the oral formulation. The methodological challenges in this study, therefore, do not undermine the main finding of less toxicity with oral vinorelbine 60 mg/m^2 than intravenous 25 mg/m^2.

Interpretation of the findings on the patients' preferences is not straightforward. The patients' lack of familiarity with the situation shortly after receiving their diagnosis

and the complexity of studying this question is challenging. Given that the expected benefits of systemic first-line treatment today are better than the threshold our patients reported, a pragmatic approach is to conduct further studies in this field later in the disease course (i.e. the second-line situation).

Implications and Implementation

The favourable toxicity profile of the VG regimen could support its use. However, the VG study had a superiority design, so we cannot conclude that VG is non-inferior to VC. The minor toxicity and HRQoL differences in favour of VG do not justify changing from a platinum regimen to a non-platinum regimen.

The oral formulation received marketing approval shortly before the VG trial, and the trial was itself instrumental in implementing oral vinorelbine for advanced NSCLC. Today, most patients in Norway receive the oral form on day 8 in the 3-week VC cycle (personal communication). This approach enables home treatment, but most centres still practice hemogram on day 8, which requires a visit to a medical facility. A trial with cisplatin and vinorelbine showed that omitting day 8 hemogram is safe [52], but whether this omitting is safe also in the VC combination is not clear. Nevertheless, oral vinorelbine saves some time for hospital staff and 'needle' and waiting time for patients, and it avoids phlebitis from vinorelbine.

Future Perspectives

The prognosis for patients with advanced NSCLC has improved substantially in the past decade due to treatments other than chemotherapy. This improvement applies both to the minority of patients with tumours with EGFR, ALK and ROS1 mutations and to the large remaining group of patients, who very clearly benefit from the drug group affecting the PD-1/PD-L1 axis. Recent milestone studies on pembrolizumab have clearly demonstrated the benefits of its implementation in first-line treatment [9, 10, 53]. Patients with > 50% PD-L1-positive tumours benefit from pembrolizumab monotherapy, and other patients with non-squamous cell histology benefit from a

combination of carboplatin-pemetrexed-pembrolizumab and from pemetrexed-pembrolizumab as maintenance treatment, while patients with squamous cell histology benefit from the combination of pembrolizumab with carboplatin and paclitaxel and from pembrolizumab as mono-maintenance

These encouraging first-line trials with pembrolizumab and chemotherapy did not include vinorelbine, so its future role in advanced NSCLC necessitates further research. One aspect in this field is that effective first-line treatment now requires multiple infusions. Patients receive maintenance treatment with a PD-1 inhibitor every third week for up to 35 cycles, and patients with adenocarcinoma also receive pemetrexed. A previous study conducted before the PD-1-inhibitor era suggested oral vinorelbine instead of pemetrexed in maintenance treatment [54]. If an oral PD-1/PD-L1 inhibitor could replace pembrolizumab, a combination with oral vinorelbine, instead of pemetrexed, could replace a huge number of infusions. However, it is not clear whether an oral PD-1-inhibitor will be available in the future [55].

Another question concerning oral vinorelbine is its potential role as a second-line treatment. Until recently, the main second-line options were docetaxel, erlotinib, and PD-1/PD-L1 axis inhibitors, and for patients with the adenocarcinoma subtype, pemetrexed. Pemetrexed and PD-1-PD-L1 axis inhibitors, as shown for pembrolizumab, have become first-line treatments, leaving docetaxel and erlotinib as second-line treatments. National guidelines in Norway do not recommend erlotinib for EGFR-negative patients, and clinical experiences with docetaxel in second-line treatments are not encouraging. Further, docetaxel's role as a post-immunotherapy drug is not yet clear. Consequently, we lack scientific evidence for an optimal second-line treatment strategy for a very large group of patients with advanced NSCLC. Whether vinorelbine will play a role as a second-line treatment for advanced NSCLC, either as a monotherapy or in combination with other agents, is not clear. However, if used as a monotherapy in second-line chemotherapy, it probably will have rather limited effects, so its use will be limited.

Patients' perspectives on benefit thresholds for accepting toxic treatment are also highly relevant in this regard.

Conclusions

1. The VG study confirms the role of a platinum combination as the main treatment in first-line treatment of advanced NSCLC.

2. The future role of vinorelbine in the treatment of advanced NSCLC is currently unclear.

3. When combined with carboplatin, the oral formulation of vinorelbine can be preferred, at least on day 8 in the 3-week cycle.

4. Patient's benefit thresholds for accepting treatment should be elicited before second-line chemotherapy for advanced NSCLC

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Paper 1-3, Informed Consent Forms, HRQoL Forms

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

Clinical Studies

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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* ⩾75 years.

Chemotherapy

Both groups were planned for three cycles of chemotherapy in 3-week cycles. Vinorelbine and gemcitabine patients received vinorelbine capsules $60 \, mg \, m^{-2}$ plus intravenous gemcitabine $1000 \, mg \, m^{-2}$, 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 $60 \, mg \, m^{-2}$ on days 1 and 8. The oral dose of vinorelbine $60 \, mg \, m^{-2}$ is comparable with the commonly used intravenous dose of $25 \, mg \, m^{-2}$ (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 $⩾1.0 \times 10^9 \, l^{-1}$ and platelets $⩾75 \times 10^9 \, l^{-1}$. The doses were reduced by 25% if ANC was $1.0–1.49 \times 10^9 \, l^{-1}$, platelets were $75–99 \times 10^9 \, l^{-1}$, or preceding nadir ANC was $<0.5 \times 10^9 \, l^{-1}$. Doses were reduced by 50% if the nadir platelet count was $<50 \times 10^9 \, l^{-1}$. 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*
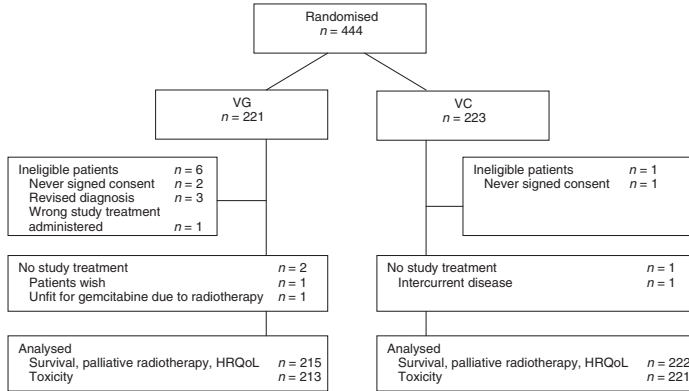
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Figure 1 CONSORT diagram.

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 <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 (VG *vs* VC) 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
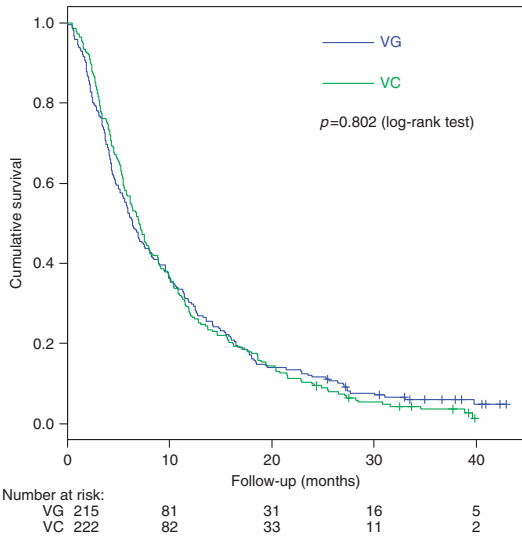
Table 2 Completion rates of the HRQoL questionnaires and mean scores for the primary HRQoL outcomes

	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.

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

CTCAE grade	VG n = 213		VC n = 221		
	No. of patients	%	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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Oral versus intravenous vinorelbine in advanced NSCLC—a retrospective comparison

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ABSTRACT

Objective: Vinorelbine combined with carboplatin is one of the recommended first-line chemotherapy regimens in advanced non-small cell lung cancer (NSCLC). Vinorelbine, traditionally administered intravenously, is also available for oral administration. However, more information regarding the efficacy of oral versus intravenous therapy is desirable. The Norwegian Lung Cancer Study Group (NLCG) conducted three first-line NSCLC trials between 2000 and 2009, which included 590 patients who received three cycles of carboplatin and vinorelbine. Two trials administered intravenous vinorelbine, and one trial administered oral vinorelbine. The aim of the current study was to compare outcomes between oral and intravenous vinorelbine in combination with carboplatin as the first-line treatment in advanced NSCLC.
Materials and methods: We retrospectively compared the survival, HRQoL and haematological toxicity between oral and intravenous vinorelbine using individual data from three trials. Eligible patients received a maximum of three 21-day cycles with intravenous carboplatin on day 1 and vinorelbine on day 1 and day 8, at doses of either 60 mg/m^2 orally or 25 mg/m^2 intravenously.
Results and conclusion: In total, 222 and 368 patients received oral or intravenous vinorelbine, respectively. The overall survival (7.0 vs. 6.9 months), chemotherapy compliance, HRQoL outcomes and toxicity were similar, although oral patients reported less worsening of constipation and had fewer adverse events of grade III–IV leukopenia and anaemia.

Oral 60 mg/m^2 vinorelbine and intravenous 25 mg/m^2 provided similar survival outcomes. HRQoL outcomes were similar or in favour of oral vinorelbine. Oral vinorelbine caused less haematological toxicity.
Microabstract: The study compares the effects of oral to intravenous vinorelbine both combined with carboplatin in advanced NSCLC. We used data from 590 patients in three previous randomized controlled trials. Survival and overall HRQoL were similar. Use of oral vinorelbine was associated with less haematological toxicity and patient reported constipation.

1. Introduction

The vinorelbine-carboplatin combination is one of the recommended first-line treatments in advanced NSCLC. Vinorelbine is available as an intravenous or oral formulation. The oral formulation allows partial home administration, thus reducing the use of hospital resources and the number of hospital visits for patients. The oral formulation also avoids the common problem of thrombophlebitis associated with intravenous vinorelbine. The advantages of oral vinorelbine in combination with carboplatin has been outlined in a recent review [1].

To date, no randomised phase III trial has directly compared oral with intravenous vinorelbine in advanced NSCLC. Moreover, the two largest randomised phase II trials administered vinorelbine as a single agent. One of these trials (189 patients) found a lower response rate with oral vinorelbine [2], while the other trial (114 patients) indicated similar response rates [3]. Only one small,

randomised trial (61 patients) has addressed the specific issue of oral versus intravenous vinorelbine in the commonly used combination with carboplatin [4]. That trial demonstrated patients' preference for oral vinorelbine, if equivalent efficacy could be presumed.

Two relatively large trials have compared oral vinorelbine with other regimens. A phase III trial (381 patients) compared an alternating intravenous day 1/oral vinorelbine day 8 regimen with docetaxel, both in combination with cisplatin, and found similar response rates and survival outcomes [5]. A phase II trial (153 patients) compared oral vinorelbine with pemetrexed, both combined with cisplatin and then continued as a single agent in maintenance therapy, and found no significant differences in response rates or survival [6].

Until now, no phase III trial has directly compared oral versus intravenous vinorelbine, and no large randomised trial has addressed the combination with carboplatin. Such a study would have to be very large; thus, alternative study designs are needed. Therefore, we assembled data from three Norwegian advanced NSCLC trials, aiming to perform a retrospective comparison of oral versus intravenous vinorelbine, both in combination with carboplatin. The current paper reports the results from this comparison.

2. Material and methods

2.1. Aim, design and approval of the study

The aim of the current study was to compare oral versus intravenous vinorelbine, both in combination with carboplatin, as first-line treatment in advanced NSCLC. The design is a retrospective comparison of individual data from three randomised chemotherapy trials [7–9]. The end points were overall survival, HRQoL, and haematological toxicity. The Regional Committee for Medical Research Ethics, Northern Norway, approved the study.

2.2. Patients and treatment

Eligible patients were those who were planned for three cycles of vinorelbine and carboplatin in the three above-mentioned trials. All patients had NSCLC stage IV or stage IIIB not eligible for curative treatment, WHO performance status (PS) 0–2, and no other clinically active malignancy. All trials allowed brain metastases and defined no upper age limit, but they required adequate bone marrow, renal, and hepatic function. All patients had undergone a baseline CT scan of the chest and upper abdomen for disease staging [10].

The first two trials [7,8] administered intravenous vinorelbine at a dose of 25 mg/m^2 at day 1 and day 8 and carboplatin according to Chatelut's formula [11] with an AUC of 4 at day 1. Antiemetic prophylaxis with intravenous dexamethasone and ondansetron on day 1 was mandatory, while it was optional at day 8.

The patients in the last trial [9] took capsules with vinorelbine at a dose of 60 mg/m^2 at days 1 and 8 along with a light meal and received carboplatin according to Calvert's formula [12] with an AUC of 5, using the Cockroft Gault formula to estimate creatinine clearance at day 1. Antiemetic prophylaxis on day 1 was the same as that in the two first trials, but the protocol recommended oral ondansetron twice on day 8.

Body surface area was calculated using the same formula in all three trials (Dubois D and Dubois EF, 1916). Patients ≥ 75 years of age received 75% of the calculated drug doses from the first cycle in the last two trials.

Before randomisation, all patients reported HRQoL on the EORTC QLQ-C30 questionnaires and the lung cancer specific QLQ-LC 13 module [13]. A central study office mailed additional questionnaires directly to the patients at 3, 6, 9 and 17 weeks (18 weeks in the first study).

Leucocyte and thrombocyte counts and haemoglobin concentration were recorded until three weeks after the last cycle. The three trials had similar rules for dose reduction or postponement of chemotherapy in cases of severe toxicity.

2.3. Analysis

We defined survival as the time from randomisation (in the patients' respective trial) until death and compared the oral and intravenous treatment groups with the Kaplan-Meier method, the log-rank test and Cox regression. CTCAE version 3.0 was used for categorising haematological toxicity, and groups were compared using a chi-squared test. HRQoL data were scored according to the EORTC scoring manual, and the group mean scores and changes in scores from baseline to each time point (score change) in each treatment group were compared using a t-test. No imputation was performed for missing values. Differences > 10 points between treatment groups were considered as clinically relevant. We also performed subgroup analyses according to age (< 75 vs. ≥ 75 years), gender, PS (0–1 vs. 2), and disease stage (IIIB vs. IV). Chemotherapy compliance was also compared in the patient subgroups defined by the baseline scores on the QLQ nausea vomiting items (absence of such symptoms vs. at least one positive score on one of the questions).

3. Results

We included 222 patients on oral vinorelbine and 368 patients on intravenous vinorelbine. The groups were demographically similar, with the exception of fewer stage IIIB patients in the oral vinorelbine group (Table 1).

The mean number of chemotherapy cycles was 2.7 in both groups. Compliance in the subgroups as defined by baseline reporting of nausea and vomiting was similar (absence of such symptoms; 2.8 cycles in both the oral and intravenous vinorelbine groups, at least one positive score; 2.6 cycles in both groups). Three patients received no study treatment (oral: one patient; intravenous: two patients) and were not included in the toxicity analysis.

The median survival was 7.0 months in the oral group and 6.9 months in the intravenous group (log rank p=0.717) (Fig. 1). A multivariate Cox regression analysis of 440 patients in the two last trials (the data from the 150 patients in the first trial lacked date for second-line treatment) detected no difference between oral vs. intravenous vinorelbine [95% CI], HR 0.97 [0.79–1.18], when adjusting for receiving vs. not receiving second-line therapy (time-dependent co-variate), HR 1.05 [0.83–1.33]; adenocarcinoma vs. other histology, HR 0.87 [0.72–1.07]; stage IIIB vs. IV, HR 0.89 [0.70–1.14]; men vs. women, HR 1.01 [0.83–1.23]; PS 0–1 vs. 2, HR 0.52 [0.41–0.64]; age ≥ 75 vs < 75, HR 0.85 [0.66–1.09].

Patients on oral vinorelbine had significantly less CTCAE grade III–IV anaemia (oral: 2.7%; IV: 5.0%; p=0.010) and leukopenia (oral: 22%; IV: 41%; p < 0.001), while the occurrence of thrombocytopenia did not differ between the treatment groups (oral: 4%; IV: 2%; p=0.264). Patients on oral vinorelbine had less leukopenia in both the gender and age subgroups, while the difference in anaemia was statistically significant only for males (Table 2).

The completion rates of the HRQoL questionnaires by week 17 were 88% and 85% in the oral and intravenous groups, respectively. No differences in the mean scores between the treatment groups exceeded 10 points (Table 3). An analysis of the change in scores showed that the patients on oral vinorelbine, compared with those on intravenous vinorelbine, reported (only statistically significant

Table 1
Baseline patient characteristics.

		Oral vinorelbine $n=222$		Intravenous vinorelbine $n=368$	
		n	%	n	%
Age					
	Median	65		65	
	Range	43–83		35–85	
	≥ 75 years	36	16	72	20
Gender					
	Male	126	57	232	63
	Female	96	43	136	37
WHO Performance Status					
	PS 0	47	21	82	22
	PS 1	119	54	181	49
	PS 2	56	25	105	29
Stage (Mountain 1997)					
	IIIB	34	15	102	28
	IV	188	85	266	72
Histology					
	Squamous cell carcinoma	45	20	104	28
	Adenocarcinoma	131	59	172	47
	Large cell carcinoma	12	5	26	7
	Other/ undifferentiated	34	15	66	18

Table 2
Grade III–IV haematological toxicity.

	Oral $n=221$		Intravenous $n=366$		
	n	%	n	%	p
Anaemia	6	3	18	6	**0.010**
Female	1	1	2	2	0.533
Male	5	4	16	7	**0.013**
≥75 year	1	3	4	6	**0.031**
<75 year	5	3	14	5	0.060
Stage IIIB	0	0	3	3	0.114
Stage IV	6	3	15	6	**0.034**
PS 0-1	2	1	12	5	**0.036**
PS 2	4	7	6	6	**0.032**
Leukopenia	49	22	150	42	**<0.001**
Female	21	22	45	34	**0.026**
Male	28	22	105	46	**<0.001**
≥75 year	5	14	35	49	**<0.001**
<75 year	44	24	115	39	**0.001**
Stage IIIB	8	24	36	36	0.332
Stage IV	41	22	114	43	**<0.001**
PS 0-1	41	25	107	41	**<0.001**
PS 2	8	15	43	41	**<0.001**
Thrombocytopenia	9	4	6	2	0.264
Female	3	3	2	2	0.081
Male	6	5	4	2	0.167
≥75 year	0	0	1	1	0.157
<75 year	9	5	5	2	0.243
Stage IIIB	0	0	3	3	0.509
Stage IV	9	5	3	1	0.086
PS 0-1	5	3	5	2	0.572
PS 2	4	7	1	1	0.115

Fig. 1. Median OS: Oral 7.0 months IV: 6,9 months log-rank $p=0.717$.

4. Discussion

In this largest comparison of oral versus intravenous vinorelbine in combination with carboplatin as first-line treatment for advanced NSCLC, we found no significant difference in survival between the two groups. The HRQoL outcomes of the groups were similar, except for some minor differences mostly in favour of the oral administration form of vinorelbine. Furthermore, fewer oral vinorelbine patients had grade III-IV leukopenia and anaemia.

Our findings are generally in accordance with those of the published literature [1]. An exception is that two previous studies [2,3] reported that compared with intravenous vinorelbine, oral vinorelbine was associated with more nausea and vomiting, which we did not observe in our study. The explanation of this difference is probably that we advised the patients on oral vinorelbine to use antiemetic prophylaxis. Furthermore, we recommended that patients combine oral vinorelbine with a light meal, as previously recommended [14]. The current study supports both recommendations.

A limitation of the current study is its retrospective design, introducing possible biases due to the inclusion of different patient populations, varying second-line therapies, and different formulas for carboplatin dosage. Furthermore, the trials did not assess response rates or progression free survival. The baseline demographic data were similar in the two populations, except for more stage IIIB patients in the intravenous group. The use of Calvert's formula with AUC 5 vs. Chatelut's formula with AUC 4 tends to result in a higher dose for women, while the effect is opposite in men (our calculations). However, the consistent findings of greater leukopenia with intravenous vinorelbine across gender and age subgroups rules out different carboplatin dosing as an explanation for greater leukopenia from intravenous vinorelbine. Because the subgroup analyses were consistent with the main findings, we consider that the methodological challenges in this study do not undermine the main findings.
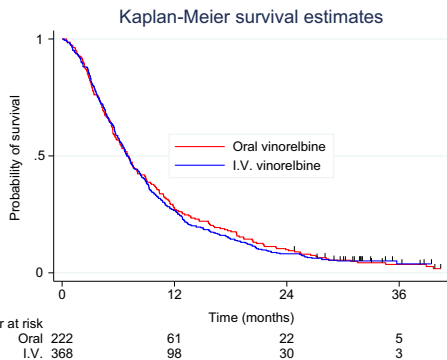
differences > 10 points are mentioned) less worsening of peripheral neuropathy at 6 and 9 weeks, constipation at 3 weeks, alopecia at 9 and 17 weeks and social functioning at 17 weeks. Additionally, patients on intravenous vinorelbine reported a greater improvement in coughing at 6 weeks. Fig. 2 shows the score changes that differed by at least 10 points on at least one time point (Fig. 2). All of the other group differences are below 10 points. Subgroup analyses according to age (<75 vs. ≥75 years), gender, PS (0–1 vs. 2), and disease stage (IIIB vs. IV) were consistent with the primary findings (data not shown).

The percentage of patients receiving at least one regimen of systemic second-line therapy (chemotherapy or TKIs) was 44% in the oral and 28% in the intravenous group.

Table 3
Completion rates of the HRQoL-questionnaires and mean scores for reported values.

	Baseline		3 weeks		6 weeks		9 weeks		17 weeks		Total	
	oral	iv	oral	iv	oral	iv	oral	iv	oral	iv	oral	iv
Alive	222	368	219	360	211	345	201	333	164	274	1017	1681
No. of delivered forms	222	358	203	315	184	303	168	269	130	204	907	1449
Completion rate (%)	100	97	93	88	87	88	84	81	79	74	88	85
Global QoL	55	51	54	55	55	52	55	53	54	51		
Physical functioning	65	62	59	58	59	57	60	58	59	57		
Role functioning	53	50	49	45	48	45	49	45	48	45		
Emotional functioning	**74**	**70***	74	75	74	75	76	76	77	73		
Cognitive functioning	81	81	79	82	82	80	80	80	81	78		
Social functioning	61	64	58	58	62	58	62	60	62	58		
Fatigue	48	49	50	51	48	52	48	51	47	48		
Nausea and vomiting	12	12	16	13	**17**	**14***	15	13	12	10		
Pain (C30-module)	35	34	33	28	31	29	31	29	32	31		
Dyspnoea	47	50	43	46	44	44	45	47	49	50		
Insomnia	34	34	30	31	27	29	27	29	28	27		
Apetite loss	33	35	36	32	33	34	30	31	32	31		
Constipation	27	23	31	37	30	34	31	36	31	27		
Diarrhoea	14	14	**17**	**12***	**16**	**11***	13	10	14	13		
Financial difficulties	10	9	9	10	10	10	8	9	9	12		
Dyspnoea (LC13-module)	40	41	40	39	36	40	**33**	**41***	**37**	**43***		
Coughing	**38**	**45****	34	35	**36**	**29***	31	31	32	35		
Heamoptysis	4	6	6	4	4	4	3	3	3	4		
Sore mouth	8	6	9	11	11	11	8	9	10	9		
Dysphagia	12	10	9	9	10	9	10	11	11	14		
Peripheral neuropathy	**16**	**11****	13	15	13	17	**13**	**20****	18	19		
Alopecia	**16**	**5****	**15**	**7****	15	12	15	14	12	16		
Pain in chest	19	22	19	21	18	22	**16**	**22***	**18**	**25***		
Pain in arm or shoulder	19	23	22	22	20	25	17	19	19	20		
Pain in other parts of body	30	28	28	27	29	27	27	29	28	28		

t-test, HRQoL = Health related Quality of life, as reported on the EORTC QLQ-C30 and LC13 modules displayed as mean scores of all reported values.
All scale scores range from 0 to 100. A high global QoL or functioning score indicates better QoL, while on the symptom scales, a higher symptom score indicate more symptoms.
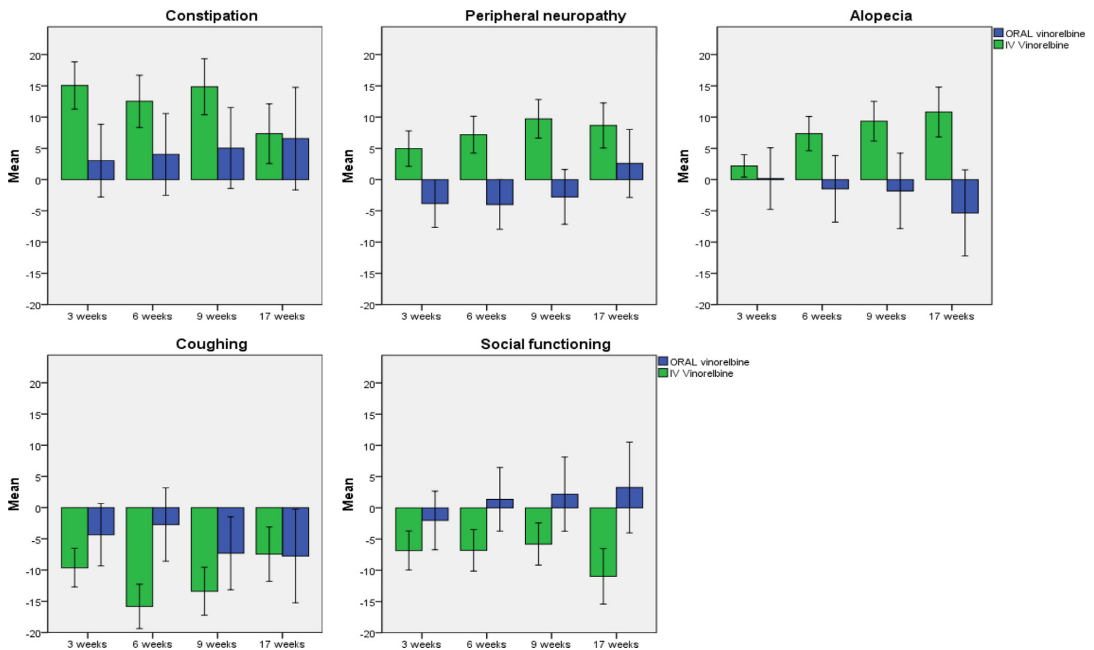
* $p < 0.05$.
** $p < 0.01$.

Fig. 2. Mean score changes in HRQoL dimensions with at least one group difference > 10 points, as reported on the EORTC QLQ-C30 form. A higher symptom score indicates more symptoms, while a a higher functioning score indicates better functioning. The error bars display 95% confidence intervals.

The high completion rate of HRQoL questionnaires throughout the treatment period in all three included trials is an important strength of this study. Moreover, to the best of our knowledge, the current study is the largest HRQoL comparison to date between oral and intravenous vinorelbine. It should be noted that patients returned the EORTC QLQ-C30 and QLQ-LC13 forms with intervals of 3 weeks, principally reporting symptoms from only the preceding week. Therefore, it is possible that the symptom burden from constipation among intravenous vinorelbine patients could have been worse shortly after the last vinorelbine administration at day 8 in every cycle. However, the available HRQoL results in our study support the conclusion that oral vinorelbine 60 mg/m², compared with intravenous 25 mg/m², is equally well tolerated.

We observed that more patients on oral than intravenous vinorelbine received second-line treatment. One main reason for this is probably that both erlotinib and pemetrexed were introduced as second-line treatments for advanced NSCLC during the interval between the two intravenous vinorelbine studies and oral vinorelbine study. One may presume that this procedure can confound survival analysis. However, the difference in the use of second-line therapy between the treatment groups was modest (44% vs. 28%), and we assume that this difference is too small to substantially influence the survival outcomes in the total study population.

Compared with recent publications on systemic treatment of NSCLC, the overall survival was poor in our study cohort. Reasons may be differences in treatment and eligibility criteria. In contrast to updated guidelines [15], maintenance treatment with pemetrexed to patients with non-squamous histology was not implemented, and the patients received only three instead of four courses of chemotherapy. We included also a large proportion of PS 2 patients, and allowed brain metastases. The impact of each of these differences is difficult to assess accurately, but they may together explain the relatively short overall survival.

Studies on the bioavailability of oral vinorelbine have shown variable results. One trial showed that the oral vinorelbine dosage of 60 mg/m² is equal to an intravenous dosage of 25 mg/m², corresponding to the reported bioavailability of 43% with the oral formulation [16]. Meanwhile, other studies have reported lower bioavailability of the oral formulation, e.g., 36–38% (Puozzo and Gridelli, 2004), 38–40% (Gebbia and Puozzo, 2005), and 27% [17]. Thus, we cannot rule out that the observation of less constipation and less leukopenia in the oral treatment group in the present study simply reflects a lower than assumed bioavailability of oral vinorelbine and that the administration form itself is not the cause for the observed differences.

A trial with cisplatin and vinorelbine in advanced NSCLC showed that the day 8 haemogram could be safely omitted in patients with PS < 2 [18]. One should, however, consider that carboplatin is more toxic than cisplatin on the bone marrow. Hence, whether a day 8 haemogram is necessary is, so far, unclear for patients receiving vinorelbine in combination with carboplatin [19]. If the day 8 haemogram can be safely omitted, it will imply that the day 8 treatment can be administered as an entirely at home treatment. Such an approach can save valuable time for both the patients and their relatives, and save hospital resources.

In summary, our retrospective comparison of oral and intravenous vinorelbine, in combination with carboplatin, showed no difference in overall survival. HRQoL outcomes were similar or in favour of oral vinorelbine. We conclude that oral 60 mg/m² vinorelbine treatment, compared with intravenous 25 mg/m², is well tolerated. Moreover, it causes fewer grades III–IV leukopenia and anaemia, and fewer patients reported worsening of constipation. Whether these differences are related to different routes of administration or differences regarding vinorelbine bioavailability is not clear.

Clinical practice points

This study is the first larger comparison of oral to intravenous vinorelbine in advanced NSCLC.

Survival and overall HRQoL in patients receiving oral was not inferior to intravenous vinorelbine.

Use of oral vinorelbine was associated with less haematological toxicity.

Clinicians can consider treating patients with advanced NSCLC with oral vinorelbine for its ease of use.

Conflicts of interest

The authors have nothing to declare.

Acknowledgements

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