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RESEARCH ARTICLE

Metronomic oral vinorelbine doublet chemotherapy with carboplatin in treatment of advanced lung cancer: a feasibility and safety study [version 1; peer review: 1 not approved]

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Abstract

Background: Non-small cell lung cancer (NSCLC) is globally one of the most common forms of cancer. Palliative treatment is a delicate balance against toxicity and survival. Using small frequent doses of chemotherapy, metronomic regimens have been hypothesized to maintain or even improve efficacy while achieving a lower treatment-related toxicity. The mechanism is thought to result from a more continuous exposure of the tumour cells to the drugs. Treating NSCLC, this study addresses the feasibility and tolerability of carboplatin in combination with 12 weeks of daily metronomic vinorelbine.

Method: Patients were included over a period of ten months. All patients had biopsy-verified incurable NSCLC and were candidates for first line chemotherapy (PD-L1<50% and no targetable mutations). This open label, non-randomized prospective safety and feasibility study was investigator initiated. Patients received up-to four cycles of standard dose carboplatin AUC 5 every third week in combination with 12 weeks of metronomic oral daily Navelbine® (20/30 mg). Patients were evaluated by CT scans after end of treatment and then every 8 weeks (+/- 1 week) until progression.

Results: A total of 20 patients were included. Male/female-ratio was 4/16. Age ranged from 49-83 with a median of 70.5 years. Majority had adenocarcinoma (95%). Two patients withdrew their consent within a week. 18 patients were included in safety analysis. 13 received all four cycles. Grade 1/2 toxicity was frequently seen and included fatigue 13 (72%), diarrhoea 13 (72%), constipation/congestion 13 (72%). Grade 3 toxicities were dyspnoea 2 (11%), nausea 3 (17%) and fatigue 3 (17%). Two (11%) had grade 4 toxicity with neutropenic fever, both recovered. No grade 5 toxicity was detected.

Conclusion: In treatment of NSCLC this study is the first addressing the regimen of carboplatin in combination with daily metronomic

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1

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vinorelbine. We conclude that doublet chemotherapy with daily vinorelbine is safe and feasible.

Keywords

NSCLC, Oral vinorelbine, Feasibility, Metronomic, Chemotherapy, Palliation, Doublet regimen, Daily

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Background

Non-small cell lung cancer (NSCLC) is the second most common cancer worldwide.¹ In Denmark 4,658 new cases were diagnosed yearly from 2012 to 2016.² The treatment goal for patients with metastatic NSCLC is to relieve symptoms and prolong survival while maintaining the best possible quality of life. Palliation, therefore, needs to be balanced against survival and toxicity. In most countries platinum based combination chemotherapy has been the standard first line treatment in NSCLC for decades, and in Denmark platinum has been used in combination with vinorelbine in NSCLC (www.dolg.dk).

When chemotherapy is given according to conventional principles, the treatment is typically given in high doses every three weeks, as the goal is to maximize the therapeutic outcome. However, because of the toxicity, there is a need for treatment-free intervals between the cycles, which could provide space and time for the development of resistant clones and regrowth of the tumour cells.³ Furthermore, the immunosuppressive effect of the chemotherapy can lead to infections and the need of antibiotic therapy and hospitalization and can ultimately be fatal.

Compared to classical cytotoxic chemotherapy, metronomic treatment regimens may have a complementary mechanism of action, targeting the tumour vasculature, thus counteracting tumour regrowth that may occur between chemotherapy cycles; in addition, metronomic chemotherapy suppresses regulatory T cells and induces the maturation of dendritic cells, thereby leading to an anti-tumour immune response.^{4,5} Metronomic regimens, in which small, frequent doses of chemotherapy are administered, have been suggested to lower treatment-associated toxicities.⁶ The high frequency of administration aims to expose tumour cells continuously to the drug, preventing recovery between cycles and possibly improving tumour control.⁷ Preclinical studies, as well as clinical observations, suggest that metronomic regimen increases the effect of a drug, not only by a direct effect on cancer cells, but also by activating endothelial cells in the tumour vasculature and thereby the tumour anti-angiogenesis. By giving smaller, but more frequent, doses of the drug, higher dose intensity, without corresponding side effects, is obtained.⁸

In a randomized phase II study, conducted in NSCLC patients, toxicity and efficacy between intravenous and oral administered vinorelbine, seemed comparable, and safety profiles of both formulations appeared to be qualitatively similar.⁹ Easy oral administration of vinorelbine, allows for flexible treatment schedules including a more frequent and metronomic dose application, and makes it an obvious candidate for metronomic studies.

Many studies have focused on comparing the efficacy of different drugs,¹⁰ but little interest has been given to the posology.^{11–16} Phase II studies with weekly intravenous vinorelbine 25–30 mg/m² as first line therapy to advanced breast cancer patients showed response rates of 41–50%, and acceptable toxicity profile.^{11–14} A previous phase I dose finding study in pre-treated NSCLC patients showed that metronomic daily oral vinorelbine as monotherapy, given in cycles of four weeks with one week of drug holiday, was safe and feasible in recommended dose level of 30–40 mg daily.¹⁷ Platinum-based doublet chemotherapy in a phase I dose finding study determined that cisplatin 85 mg/m² every third week in combination with oral vinorelbine 60 mg three times weekly was feasible and active in advanced NSCLC.¹⁶ Upon registration of a drug there is often limited knowledge of the best dosing and there could be much to gain in this field. Metronomic chemotherapy is not yet well validated in the clinic, and the optimal dosage and regimens are yet to be identified.

There are no published studies with daily oral vinorelbine in combination with carboplatin for treatment of patients with advanced non-small cell lung cancer. The current study aims to test a daily dosage of vinorelbine 20/30 milligram (mg) in combination with carboplatin focusing on the safety aspect and tolerability. If this outcome is achieved this dosing schedule would be usable in future randomised combination studies with carboplatin including maintenance arm with vinorelbine in lung cancer treatment.

Methods

Study design

This study was investigator-initiated and designed as a prospective non-randomized, open-label, single site, safety, and feasibility study. It was planned to recruit 20 patients. Patients with incurable NSCLC, who were chemo-naïve and candidates for 1st-line chemotherapy (PD-L1 < 50%), were included. Patients included in the study received standard dose of carboplatin AUC 5 every 3rd week and metronomic oral Navelbine® (20/30 mg) daily for 12 weeks. After four cycles of chemotherapy, if partial response or stable disease, patients with non-squamous carcinoma received pemetrexed as maintenance chemotherapy according to national standard treatment recommendation (www.dolg.dk). Patients were followed by computer tomography (CT) scans for evaluation every second month and evaluated according to Response Evaluation Criteria In Solid Tumours (RECIST).¹⁸ The study design is shown in [Figure 1](#). Each patient received first cycle as carboplatin AUC 5 day 1 and Navelbine® 20 mg daily in first 3 weeks, and if there was acceptable toxicity, the dose of Navelbine® was escalated to 30 mg daily. A maximum of four cycles were delivered. For safety reason the first six

Figure 1. Study design.

patients enrolled had World Health Organisation (WHO) performance status (PS) 0-1. The next fourteen patients included were allowed to have PS 0-2.

There was incorporated an interim analysis in the study. We proceeded with the analysis when the 10th patient had received 2 cycles (6 weeks) of treatment or if 4 patients experienced an unacceptable toxicity (UT; see definition in appendix A in extended data in figshare datafile¹⁹), despite the dose reduction of Navelbine and carboplatin or in case of any grade 5 toxicity.

Dose adjustment plan and definition: A dose adjustment of chemotherapy was permitted according to treatment modification guidelines at the Department of Oncology, Aarhus University Hospital (see guidelines for treatment modification in appendix A in extended data in figshare datafile¹⁹). Dose adjustment was allowed in the case of significant haematological and/or non-haematological toxicity. Generally, dose adjustment and/or treatment delay was decided at the respective visit based on symptoms, physical examination and haematological values (see Dose Adjustment section, appendix A in extended data in figshare datafile¹⁹).

Patients were instructed to report any toxicity that occurred between cycles or in between visits. Moreover, during the entire treatment period patients kept a diary. They registered dose and time of taking Navelbine and brought their diary on every visit. The patients were asked to register any adverse event in the diary. There were scheduled five visits during the 12 weeks of treatment. Regarding antiemetics there were no restrictions. Metoclopramide was given in addition to the standard antiemetics (oral prednisolone 75 mg day 1, 50 mg day 3-4 and 25 mg day 5; aprepitant 125 mg day 1, 80 mg day 2-3 and ondansetron 16 mg day 1-2), when treating with a standard carboplatin and vinorelbine regimen. Significant effort has gone into using the same antiemetics across patients in the study.

Safety assessment: Symptoms and haematological values were measured at baseline and then every third week during the four cycles. Additional haematological values were measured at day 12 ± 2 during the first cycle to register any haematological side effects. If haematological toxicity occurred the patient was contacted by telephone.

All toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.03), during the first 84 days (12 weeks) of the treatment period. Toxicity was registered as patient-reported outcome (via online records/AmbuFlex[®]), every 3rd week during the treatment period. The focus was on the following: febrile neutropenia, neutropenia (reported only by study-nurse or physician according to blood tests), any fever, hospitalization, vomiting, diarrhoea, stomatitis, anorexia, dyspnoea, weight loss, thromboembolic events and any other adverse events. All unacceptable toxicities (UTs) such as febrile neutropenia, thrombocytopenia or any non-haematological grade 3 and 4 toxicity were defined (see unacceptable toxicities (UTs), appendix A in extended data in figshare datafile¹⁹).

Ethical issues

This study was designed and performed according to the fifth version of the Declaration of Helsinki, the protocol, ICH-GCP guidelines and national laws. The protocol was approved by the Research Ethics Committee case no.: 1-10-72-187-17; the Danish Data Protection Agency (Datatilsynet) case no.: 1-16-02-741-17; the national Medical Products Agency no.: 2017083768; with EUDRACT no.: 2017-000659-23; <https://www.clinicaltrialsregister.eu/ctr-search/search?query=2017-000659-23>, and monitored by the GCP unit, Aarhus university, Denmark.

Patient records and case report forms obtained during the study, were archived by the oncology department and at the Clinical Research Unit, Aarhus University Hospital, for at least 5 years after the completion. The study was conducted respecting the patient's physical and mental integrity and privacy. The investigator ensured that each study patient was fully informed about

the nature and objectives of the study and possible risks associated with participation. The investigator and the co-investigators obtained written informed consent from each patient before any study-specific activity was performed.

Statistical methods

Sample size calculation

The objective of this study is to evaluate the safety and feasibility of a combination of carboplatin AUC 5 every 3rd week with vinorelbine 20/30 mg daily during 12 weeks in patients with advanced or metastatic NSCLC. Assuming overall sample size of around 200 patients in a future randomised phase II study with the same study design we will need about 10% of overall sample size to examine safety and feasibility. In this study we estimated that 20 patients would be sufficient to give the information about the safety and feasibility of metronomic therapy in combination with carboplatin, when using the Simon's Two-Stage for phase II clinical trial.²⁰

Continuous data is summarized with the following items: frequency, median, (if $n \geq 3$), range and mean. Characteristics of the disease at diagnosis and demographic data at baseline was tabulated on all included patients.

Overall survival (OS) for the whole group was calculated using the Kaplan-Meier method. Progression free survival was calculated from date of inclusion until progression. OS was measured from the date of inclusion just before starting the first line chemotherapy until the date of death from any cause or the last date the patient was known to be alive. OS analyses were carried out using STATA version 16 (Stata, RRID:SCR_012763); an open-access alternative is R (<https://www.r-project.org/>).

Results

20 patients with inoperable or disseminated, pathologically proven NSCLC, from May 2018 to February 2019, were included. The median age was 70.5 years (range 49-83). 19 patients (95%) had adenocarcinoma. Patient characteristics are shown in Table 1. Two patients withdrew their consent within one week; one decided not to receive any palliative

Table 1. Patient characteristics in intent to treat population.

	no (N = 20)	(%)
Gender		
Male	4	(20)
Female	16	(80)
Age, median (range)	70.5 (49-82)	
Histology		
Adenocarcinoma	19	(95)
Squamous	1	(5)
Stage		
III	1	(5)
IV	19	(95)
WHO performance status		
0	7	(35)
1	11	(55)
2	2	(10)
Smoking status		
Smokers	6	(30)
Former smokers	14	(70)
PD-L1 status*		
≤50%	0	(0)
≤20%	5	(25)
<1%	15	(75)

*PD-L1, Programmed Cell Death Ligand 1.

treatment; the other decided to receive standard treatment, as the patient could not cope with protocol requiring an extra blood sample during the first cycle. These two patients are only included in the intent-to-treat population in the overall survival analyses.

18 patients were evaluable for toxicity analysis as shown in the flowchart in [Figure 2](#). These eighteen patients received a total of 62 cycles of carboplatin in addition to daily oral vinorelbine. The median dosage of oral vinorelbine received per patient was 1780 mg (range 260-2370 mg). 13 patients received all four cycles of chemotherapy (see appendix B, fig 5 in extended data in figshare datafile²¹). One patient received only three cycles, as the physician clinically suspected progression, although the following evaluating CT-scan showed stable disease. Four patients received only 1-2 cycles of chemotherapy; one patient had clinical progression (without verifying CT scan); one patient had decline in PS and was terminated from study (see flowchart, [Figure 2](#)); two patients had clinical disease progression during the treatment time and performed an evaluation CT scan in advance.

The majority of patients had grade 1 or 2 toxicity. Frequent toxicities (any grade) included fatigue 13 (72%), diarrhoea 13 (72%), constipation 13 (72%), nausea 9 (50%) and dyspnoea 12 (67%). Some patients had more than one toxicity. Grade 3 toxicities were dyspnoea 2 (11%), nausea 3 (17%) and fatigue 3 (17%) as shown in toxicity [Table 2](#). These mentioned toxicities led to a brief break in daily vinorelbine intake and dose reduction according to dose adjustment

Figure 2. Study flowchart.

Table 2. Toxicity profile in all patients who received one or more cycles of treatment.

Adverse event (AE)	Any grade n=18 (%)	Grade 3	Grade 4
Haematological			
ALAT increased	2 (11.1%)		
Anaemia	3 (16.7%)		
BASP increased	3 (16.7%)		
Febrile neutropenia	2 (11.1%)		2 (11.1%)
Platelet count decreased	1 (5.6%)		
Hyponatremia	2 (11.1%)		
GFR decreased	1 (5.6%)		
Non-haematological			
Fatigue	13 (72.2%)	3 (16.7%)	
Constipation	13 (72.2%)		
Diarrhoea	13 (72.2%)		
Vomiting	2 (11.1%)	1 (5.6%)	
Nausea	9 (50.0%)	3 (16.7%)	
Dyspepsia	1 (5.6%)		
Dysphagia	1 (5.6%)		
Dyspnoea	12 (66.7%)	2 (11.1%)	
Cough	5 (27.8%)		
Dehydration	1 (5.6%)	1 (5.6%)	
Oedema	1 (5.6%)		
Fever	3 (16.7%)		
Haemoptysis	1 (5.6%)		
Infection	1 (5.6%)	1 (5.6%)	
Metastasis, subcutaneous	1 (5.6%)		
Mucositis oral	3 (16.7%)		
Pain	6 (33.3%)		
Peripheral neuropathy	4 (22.2%)		
Hearing impaired	2 (11.1%)		
Tinnitus	1 (5.6%)		
Tumour pain	6 (33.3%)	1 (5.6%)	

Some patients had more than one adverse event.

guidelines (in appendix A in extended data in figshare datafile).¹⁹ Two patients (11%) had febrile neutropenia as a grade 4 toxicity: one patient recovered after three weeks and continued the treatment in reduced dose; the other patient recovered after six days, but did not receive any treatment hereafter, according to investigator's decision, as the PS disqualified the patient from any further treatment (exacerbation of patient's chronic obstructive lung disease). Both febrile neutropenia events occurred at day 12 and 13 after the first cycle, respectively. None of the patients included in the study had cumulative haematological toxicity. No patients in the study had grade 5 toxicity.

Six (46%) of the thirteen patients who received all four cycles did not have reduction in vinorelbine doses (20/30 mg), even though the total dosage varies per patient from 2200-2370 mg, as treatment cycle period varied from 19-23 days. Five patients received a reduced dosage of vinorelbine from the second cycle (stayed at 20 mg without dose escalation to 30 mg): one patient had a single rise in alanine aminotransferase (ALT) grade 2 at first cycle; one had diarrhoea grade 2; one had fatigue and weight loss grade 3; one had dose interruption in first cycle because of febrile neutropenia grade 4 and started the second cycle at 20 mg (a dose reduction) and one patient continued at 20 mg in all treatment periods, because of

the patient's age, 80 years (physician's decision). Two patients received full doses of chemotherapy up to the third cycle but had an interruption of 3-5 days in vinorelbine intake at the end of the fourth cycle, because of fatigue and nausea grade 2. Four patients did not receive more than 1 to 2 cycles due to degrading in PS and/or disease progression as mentioned above.

The total dose of vinorelbine administered per patient per cycle and response characteristics is shown in appendix B, fig 5, in extended data in figshare datafile.²¹

Median follow-up time was 22.1 months (95% CI: 18.9 – 25.2 months). At the end of the study, four patients were alive. Sixteen patients had eligible progression free survival (PFS) data for analysis. Median PFS was 4.8 months (95% CI: 4.3 – 5.2 months). Median overall survival was 14.1 months (95% CI: 5.9 – 18.6 months) for the entire population, see Figure 3. Five patients (28%) out of 18 patients had partial response (PR), and six patients (33%) had stable disease (SD). Five patients (28%) had progressive disease (PD) in evaluation scans. One of these patients had regression in target lesion but was considered PD because of newly developed malignant pleural exudate (as marked with asterisk in the waterfall plot, Figure 4). Two patients could not go through evaluation with CT scans, but developed clinical symptoms of progression and decline in PS. Response rate (RR) in this feasibility and safety study was 61% (11 out of 18 patients).

Discussion

This study showed that metronomic oral vinorelbine 20/30 mg daily in combination with carboplatin AUC 5 was safe and feasible. The most frequent toxicities such as fatigue, diarrhoea, and constipations have been manageable.

Oral vinorelbine as metronomic monotherapy has been evaluated, using different dose regimens, such as fractionated regimen (day 1, 3 and 5) and daily intake.^{22–26} In patients with NSCLC the daily intake of oral vinorelbine up to 40 mg, as monotherapy, was well-tolerated.^{22,23} In a study, Tufman et al. showed no relevant accumulation in the pharmacokinetic analysis, using vinorelbine as monotherapy in a daily dosing of 30-40 mg.¹⁵ Oral vinorelbine is rapidly absorbed at 80 mg/m² (Tmax 1.4 ± 0.7 hours) and shows a bioavailability of 43% ± 14%.⁸ The absorption is not affected to a significant extent by food.²⁷

Other studies have focused on metronomic oral vinorelbine as combination chemotherapy. A dose finding phase I doublet chemotherapy study of oral vinorelbine 50 mg 3 times weekly in combination with cisplatin 80 mg/m² (day 1 every 3 weeks) showed no haematological toxicities. With escalation of vinorelbine up to 70 mg 3 times weekly plus 85 mg/m² cisplatin per cycle, grade 3 or 4 toxicities were dose limiting.¹⁶ The Hellenic Oncology Research Group (HORG), in a

Figure 3. Kaplan-Meier curve for overall survival in intent to treat population (n = 20).

Figure 4. Waterfall plot shows responses in 16 patients, all with evaluation CT scans. *Patient had regression in evaluable target lesion, but CT scan showed a new lesion: malignant pleural exudate.

phase II study, evaluated the safety and efficacy of metronomic vinorelbine in combination with cisplatin as first line treatment in patients with advanced NSCLC.²⁸ Patients were treated with cisplatin (80 mg/m²) in combination with oral metronomic vinorelbine (60 mg, three times weekly) in cycles of 21 days. They reported myelosuppression as the main adverse event with grade 3 and 4 neutropenia occurring in five (14.3%) and six (17.1%) patients, respectively.²⁸

Several breast cancer studies, with metronomic vinorelbine concomitant with capecitabine, have also found that vinorelbine three times weekly is safe and has unchanged efficacy.^{29–31} Two of these studies indicate that it might be possible to improve both efficacy and safety with daily metronomic therapy.

There are no published studies of daily oral vinorelbine, without any planned break, in combination with carboplatin for treatment of NSCLC.

In the current study, we examined whether the doublet chemotherapy with carboplatin every third week concomitant with daily oral vinorelbine in 12 weeks was safe and feasible. Fatigue, constipation, and diarrhoea grade 2 was the most frequent reason for short interruptions in daily intake or dose reduction of vinorelbine to 20 mg daily. We found that the above-mentioned doublet regimen in treatment of NSCLC patients is feasible with both 20 mg daily with escalation to 30 mg daily or only 20 mg daily in the entire treatment period. The observed partial response or stable disease (in 11 out of 18 patients) and disease progression were not correlated with the daily dose of vinorelbine as shown in appendix B, fig 5, in extended data in figshare datafile.²¹ The study design, carboplatin in combination with daily oral vinorelbine 20 mg (or 20/30 mg) without planned breaks, could be useful in future studies, that includes metronomic doublet regimens.

During the first cycle haematological quantities were also measured at day 12 ± 2 and showed no significant reduction in neutrophil counts. Therefore, routine measuring of haematological quantities at day 12 ± 2 in the first cycle may not be necessary. The tolerability profile, with grade 3; fatigue 17%, nausea 17%, grade 4; febrile neutropenia 11% and no grade 5 toxicity, was acceptable and comparable with historical doublet regimen with cisplatin every third week and metronomic vinorelbine 60 mg, 3 times weekly, in first line chemotherapy in NSCLC.²⁸ Progression free survival of

4.8 months in this study was comparable with other studies using platinum based standard doublet treatments with vinorelbine (PFS: 4.2 months) or pemetrexed (PFS: 4.3 months).³²

This study was designed to determine the safety and clinical feasibility and was not powered to conclude on efficacy. Therefore, the trend of higher RR and longer OS is associated with a high level of uncertainty.

In conclusion, carboplatin in combination with metronomic daily oral vinorelbine 20/30 mg without any pre-planned breaks is a safe and feasible option in the treatment of patients with NSCLC. The toxicity rates, PFS and OS were comparable with standard regimens.

Data availability

Underlying data

Figshare: Underlying data for 'Metronomic oral vinorelbine doublet chemotherapy with carboplatin in treatment of advanced lung cancer: a feasibility and safety study'. <https://doi.org/10.6084/m9.figshare.14849760.v1>³³

This project contains the following underlying data.

- F1000Res NavMetroData.xlsx (Complete raw demographic and clinical information for each patient included in this study).

Reporting guidelines

Figshare: CONSORT and TREND checklists for 'Metronomic oral vinorelbine doublet chemotherapy with carboplatin in treatment of advanced lung cancer: a feasibility and safety study'. <https://doi.org/10.6084/m9.figshare.14958543>

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

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References

1. Society T.A.C.: **Key Statistics for Lung Cancer**. 2017. [Reference Source](#)
2. Bekæmpelse K: **Kort om lungekræft**. [Reference Source](#)
3. Gregory RK, Smith IE: **Vinorelbine--a clinical review**. *Br J Cancer*. 2000; **82**(12): 1907–1913. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
4. Kerbel RS, Kamen BA: **The anti-angiogenic basis of metronomic chemotherapy**. *Nat Rev Cancer*. 2004; **4**(6): 423–436. [PubMed Abstract](#) | [Publisher Full Text](#)
5. Torimura T, et al.: **Metronomic chemotherapy: possible clinical application in advanced hepatocellular carcinoma**. *Transl Oncol*. 2013; **6**(5): 511–519. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
6. Wichmann V, et al.: **Recent clinical evidence on metronomic dosing in controlled clinical trials: a systematic literature review**. *Acta Oncol*. 2020; **59**(7): 775–785. [PubMed Abstract](#) | [Publisher Full Text](#)
7. Barletta G, et al.: **Oral vinorelbine in the treatment of non-small-cell lung cancer**. *Expert Opin Pharmacother*. 2014; **15**(11): 1585–1599. [PubMed Abstract](#) | [Publisher Full Text](#)
8. Marty M, et al.: **Oral vinorelbine pharmacokinetics and absolute bioavailability study in patients with solid tumors**. *Ann Oncol*. 2001; **12**(11): 1643–1649. [PubMed Abstract](#) | [Publisher Full Text](#)
9. Jassem J, et al.: **A multicenter randomized phase II study of oral vs. intravenous vinorelbine in advanced non-small-cell lung cancer patients**. *Ann Oncol*. 2001; **12**(10): 1375–1381. [PubMed Abstract](#) | [Publisher Full Text](#)
10. Schiller JH: **Current standards of care in small-cell and non-small-cell lung cancer**. *Oncology*. 2001; **61**(Suppl 1): 3–13. [PubMed Abstract](#) | [Publisher Full Text](#)
11. Fumoleau P, et al.: **Phase II trial of weekly intravenous vinorelbine in first-line advanced breast cancer chemotherapy**. *J Clin Oncol*. 1993; **11**(7): 1245–1252. [PubMed Abstract](#) | [Publisher Full Text](#)
12. García-Conde J, et al.: **Phase II trial of weekly IV vinorelbine in first-line advanced breast cancer chemotherapy**. *Ann Oncol*. 1994; **5**(9): 854–857. [PubMed Abstract](#) | [Publisher Full Text](#)
13. Twelves CJ, et al.: **A phase II, multicentre, UK study of vinorelbine in advanced breast cancer**. *Br J Cancer*. 1994; **70**(5): 990–993. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
14. Bruno S, et al.: **Phase II trial of weekly i.v. vinorelbine as a single agent in first-line advanced breast cancer chemotherapy**. The

- Latin-American experience.** *Am J Clin Oncol.* 1995; **18**(5): 392–396.
[PubMed Abstract](#) | [Publisher Full Text](#)
15. Tufman A, *et al.*: **Treatment of advanced recurrent NSCLC with daily oral vinorelbine: A phase I trial.** *J Clin Oncol.* 2013; **31**(15_suppl): e19108–e19108.
[PubMed Abstract](#) | [Publisher Full Text](#)
 16. Pallis AG, *et al.*: **A multicenter phase I trial of metronomic oral vinorelbine plus cisplatin in patients with NSCLC.** *Cancer Chemother Pharmacol.* 2011; **67**(6): 1239–1245.
[PubMed Abstract](#) | [Publisher Full Text](#)
 17. Guetz S, *et al.*: **Metronomic treatment of advanced non-small-cell lung cancer with daily oral vinorelbine – a Phase I trial.** *Onco Targets Ther.* 2017; **10**: 1081–1089.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 18. Eisenhauer EA, *et al.*: **New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).** *Eur J Cancer.* 2009; **45**(2): 228–247.
[PubMed Abstract](#) | [Publisher Full Text](#)
 19. Kandi M: **Toxicity and dose adjustment: Definition of Unacceptable Toxicity (UT) and guideline for treatment modification at department of oncology in Aarhus, Denmark.** 2009; **45**(2): 228–247.
[PubMed Abstract](#) | [Publisher Full Text](#)
 20. Simon R: **Optimal two-stage designs for phase II clinical trials.** *Control Clin Trials.* 1989; **10**(1): 1–10.
[PubMed Abstract](#) | [Publisher Full Text](#)
 21. Kandi M: **Total dose of vinorelbine administered per patient per cycle and response characteristic.**
[Publisher Full Text](#)
 22. Tufman A, *et al.*: **Tumor conference II.** *Onkologie.* 2013; **36**(Suppl 6): 14–16.
 23. Addeo R, *et al.*: **Low-dose metronomic oral administration of vinorelbine in the first-line treatment of elderly patients with metastatic breast cancer.** *Clin Breast Cancer.* 2010; **10**(4): 301–306.
[PubMed Abstract](#) | [Publisher Full Text](#)
 24. Briassoulis E, *et al.*: **Dose selection trial of metronomic oral vinorelbine monotherapy in patients with metastatic cancer: a hellenic cooperative oncology group clinical translational study.** *BMC Cancer.* 2013; **13**: 263.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 25. Camerini A, *et al.*: **Metronomic oral vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer: results of a phase II trial (MOVE trial).** *BMC Cancer.* 2015; **15**: 359.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 26. Kontopodis E, *et al.*: **A phase II study of metronomic oral vinorelbine administered in the second line and beyond in non-small cell lung cancer (NSCLC): a phase II study of the Hellenic Oncology Research Group.** *J Chemother.* 2013; **25**(1): 49–55.
[PubMed Abstract](#) | [Publisher Full Text](#)
 27. Bugat R, *et al.*: **The effects of food on the pharmacokinetic profile of oral vinorelbine.** *Cancer Chemother Pharmacol.* 2002; **50**(4): 285–290.
[PubMed Abstract](#) | [Publisher Full Text](#)
 28. Katsaounis P, *et al.*: **Cisplatin in combination with metronomic vinorelbine as front-line treatment in advanced non-small cell lung cancer: a multicenter phase II study of the Hellenic Oncology Research Group (HORG).** *Cancer Chemother Pharmacol.* 2015; **75**(4): 821–827.
[PubMed Abstract](#) | [Publisher Full Text](#)
 29. Cazzaniga ME, *et al.*: **Efficacy and Safety of the All-Oral Schedule of Metronomic Vinorelbine and Capecitabine in Locally Advanced or Metastatic Breast Cancer Patients: The Phase I-II VICTOR-1 Study.** *Int J Breast Cancer.* 2014. **2014**: p. 769790.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 30. Langkjer S, *et al.*: **First Line therapy of metastatic or locally advanced HER2-positive breast cancer.** *Update of the HERNATA study.* 2013.
 31. Brems-Eskildsen AS, *et al.*: **Metronomic treatment of vinorelbine with oral capecitabine is tolerable in the randomized Phase 2 study XeNa including patients with HER2 non-amplified metastatic breast cancer.** *Acta Oncol.* 2020: 1–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 32. Bennouna J, *et al.*: **Oral vinorelbine plus cisplatin as first-line chemotherapy in nonsquamous non-small-cell lung cancer: final results of an International randomized phase II study (NAVotrial 01).** *Clin Lung Cancer.* 2014; **15**(4): 258–265.
[PubMed Abstract](#) | [Publisher Full Text](#)

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Christos Chouaid

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This study, which concerns the tolerance of the Carboplatinvinorelbine metronomic combination, is well conducted but its clinical impact is very low given the use of anti-PD1 / PDL1 in first line.

The authors should at least in a paragraph discussing this limitation in a hexaustic way, cite the studies (i.e. Vergnenegre *et al.* (2020¹)) which tested the combination vinorelbine metronomic Immunotherapy and also state what is the clinical impact of their study according to current recommendations.

References

1. Vergnenegre A, Monnet I, Bizieux A, Bernardi M, et al.: Open-label Phase II trial to evaluate safety and efficacy of second-line metronomic oral vinorelbine-atezolizumab combination for stage-IV non-small-cell lung cancer - VinMetAtezo trial, (GFPC# 04-2017). *Future Oncol.* 2020; **16** (4): 5-10 [PubMed Abstract](#) | [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: thoraci oncology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 12 Feb 2022

Maria Kandi, Aarhus University Hospital, Aarhus N, Denmark

Dear Prof. Chouaid,

On behalf of the authors I would like to thank you for both your time spent on reviewing our manuscript and the constructive comments.

Below you can see our response to your comments:

At the time we conducted this safety and pilot study the 1. line treatment of NSCLC with PD-L1 status under 50%, in Denmark, was carboplatin and vinorelbine day 1 and 8 every third week x 4 with optional pemetrexed as maintenance. In February 2020 the national recommendation changed toward giving immunotherapy to non-squamous NSCLC in combination with chemotherapy (carboplatin and pemetrexed) as standard. Ultimo 2020 the national recommendation changed again in favor of triple therapy for all adenocarcinomas regardless of PD-L1 status.

This pilot study shows that the combination of carboplatin and metronomic vinorelbine is safe and feasible. The regimen could be used in future studies using combinations of carboplatin + metronomic vinorelbine + immunotherapy (e.g. phase II trials: 1. line carboplatin + metronomic vinorelbine + immunotherapy versus carboplatin + pemetrexed/paclitaxel + immunotherapy in patients with PD-L1 status under 50 %).

With kind regards

Maria Kandi

Corresponding author

Competing Interests: No competing interests were disclosed.

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