VIA MEDICA

REVIEW ARTICLE

Magdalena Knetki-Wróblewska[1, 2], Maciej Krzakowski[1, 2]

[1]Department of Lung Cancer and Thoracic Tumours, Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw
[2]Department of Gastroenterology, Hepatology, and Oncology, Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw & Centre of Postgraduate Medical Education, Warsaw

Metronomic chemotherapy in non-small-cell lung cancer — current status

Address for correspondence:
Lek. Magdalena Knetki-Wróblewska
Klinika Nowotworów Płuca i Klatki Piersiowej
Centrum Onkologii — Instytut w Warszawie
e-mail: magdalena.knetki@coi.pl

Oncology in Clinical Practice
2016, Vol. 12, No. 2, 37–42
Translation: dr n. med. Dariusz Stencel

ISSN 2450–1654

ABSTRACT

Chemotherapy remains a standard treatment of advanced non-small-cell lung cancer. Metronomic chemotherapy – frequent administration of low-dose cytotoxic agents – may be a new option with minimal toxicity. This method may have complex mechanisms of action — the antiangiogenic effects and modulation of the immune system are crucial. Vinorelbine could be an option for non-small-cell lung cancer patients because of it has favourable safety profile and the oral form of the drug is easy to administer. There are some studies documenting the clinical activity of oral vinorelbine in advanced non-small-cell lung cancer patients. However, further prospective studies are necessary to assess the place of metronomic chemotherapy in clinical practice.

Key words: metronomic, NSCLC, vinorelbine

Oncol Clin Pract 2016; 12, 2: 37–42

Introduction

Palliative chemotherapy is a standard of care in patients with advanced non-small-cell lung cancer (NSCLC) without activating mutations in the *EGFR* gene. Platinum-based doublet chemotherapy could be considered in patients with satisfactory performance status without significant comorbidities. In elderly patients or in case of worse performance status, either monotherapy (most frequently vinorelbine or gemcitabine) or best supportive care (BSC) should be considered [1]. According to the standard schedules of administration of cytotoxic drugs, they should be administered in maximum tolerated doses in 21-day cycles [1]. The duration of time intervals between subsequent chemotherapy cycles results mainly from the necessity to recover from myelosuppression. At the same time there are some changes observed in stroma and blood vessels of cancer, which adversely influence the final treatment efficacy and consequently could lead to resistance to chemotherapy [2]. Regeneration of endothelium of cancer vasculature is the main mechanism causing these effect. It was observed that more frequent administration of some cytotoxic drugs (e.g. cyclophosphamide, methotrexate, gemcitabine, and vinorelbine) in lower doses could have an antiangiogenic affect [3, 4]. This pattern of cytotoxic drugs administration was named metronomic chemotherapy, and the last two years brought new evidence on the mechanism of action, anticancer effectiveness, and safety of this method.

The majority of published data regarding metronomic chemotherapy is based on experience in patients with breast cancer, NSCLC and prostate cancer [5]. The use of vinorelbine in patients with advanced NSCLC is of the highest importance.

This review presents theoretical rationale underlying metronomic chemotherapy and available data on metronomic chemotherapy with the use of oral vinorelbine in patients with advanced NSCLC.

Mechanism of action of metronomic chemotherapy

The efficacy of metronomic chemotherapy, to a very limited extent, depends on direct cytotoxic activity, and a major role is played by antiangiogenic and immunomodulatory effects [6].

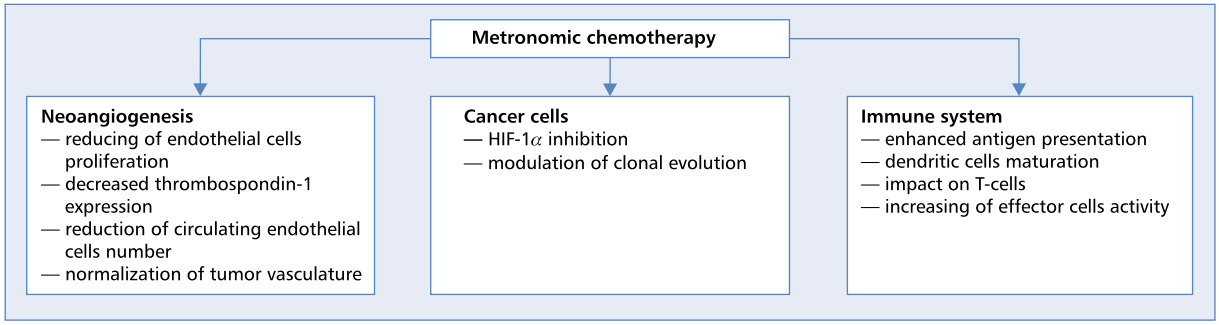

Figure 1. Metronomic chemotherapy — mechanisms of action (based on [2])

Antiangiogenic effect

The antiangiogenic effect is related to impaired function of endothelial cells of cancer blood vessels, leading to inhibition of their proliferation and migration as well as to induction of apoptosis [3, 4]. Increased thrombospondin-1 (TSP-1) level, a protein potently inhibiting angiogenesis, is also responsible. Thrombospondin-1 inhibits angiogenesis directly in connection with induction of apoptosis and inhibition of migration of endothelial cells, and indirectly though growth factor [7]. Lower mobilisation of progenitor endothelial cells from bone marrow is also observed [5].

Immunomodulatory effect

Recent years have brought important progress in immunotherapy of cancers, and the efficacy of immunocompetent drugs (so called checkpoint inhibitors — e.g. ipilimumab, nivolumab, pembrolizumab) in some malignancies (e.g. NSCLC, melanoma) has already been established. Although the anticancer activity of cytotoxic drugs is based on their direct influence on cancer cells, they are also able to modulate immune system functions. Metronomic chemotherapy could enhance the immunomodulatory effect with minimal immunosuppression [2]. Among the mechanisms responsible for such effects are induction of immune-dependent apoptosis, increased antigen presentation by dendritic cells, and intensification of cancer cell immunogenicity. Additionally, decreasing regulatory T-cell numbers are observed. Long-term stimulation of the effects that are beneficial for anticancer treatment could allow prolongation of the time of cancer control. A synergistic effect of metronomic chemotherapy and immunocompetent drugs was also suggested [2].

Vinorelbine

Vinorelbine is a member of the vinca alkaloids family of cytotoxic drugs. It binds to mitotic microtubules and inhibits cell cycle in the G2-M phase, leading to death of the cell within the interphase or any subsequent mitotic stage [8]. There are two available forms of the drug: intravenous and oral (estimated bioavailability of oral vinorelbine is appeoximately 40%). The mean half-life of the drug is about 40 hours; however, the half-life of the active metabolite (4-O-deacetylvinorelbine) is up to 168 hours [9]. Vinorelbine is metabolised in the liver through CYP3A4 cytochrome and is excreted with bile. It is recommended that entire vinorelbine capsules are swallowed with a small amount of water [10].

Standard chemotherapy

Vinorelbine was initially used intravenously only in NSCLC patients, and its effectiveness was confirmed in palliative chemotherapy (either monotherapy or platinum-based doublets) as well as in treatment combined with radical therapy modalities (chemo-radiotherapy, postoperative adjuvant chemotherapy with platinum-based doublets). Development of the oral form of vinorelbine led to establishment of an optimal dosing schedule and then the conduction of clinical trials assessing the efficacy and safety of the drug. It was determined that an intravenous dose of 30 mg/m^2 is equal to an oral dose of 80 mg, and a dose of 25 mg/m^2 is equal to an oral dose of 60 mg. It was also stated that the optimal schedule of oral vinorelbine dosing is to administer a dose of 60 mg/m^2 in the first cycle (days 1, 8, and 15) and dose escalation is possible up to 80 mg/m^2 in patients with acceptable toleration of the treatment (mainly haematological) [11, 12].

A total of 115 patients with advanced NSCLC were enrolled to prospective phase II clinical trials with the primary endpoint to assess objective response rate (ORR). Progression-free survival (PFS), overall survival (OS), and safety profile of both forms of vinorelbine were also evaluated [12]. It was shown that the efficacy of oral and intravenous vinorelbine form was comparable in reference to ORR (14% vs. 12%). Median PFS was 3.2 and 2.1 months, respectively, and median of survival time was 9.3 months and 7.9 months, respectively. Small differences in toxicity profiles of both forms of vinorelbine were observed.

Table 1. Side effects of vinorelbine used in standard dosage (based on [12])

	Oral vinorelbine		Intravenous vinorelbine	
	Total (%)	Grade 3–4 (%)	Total (%)	Grade 3–4 (%)
Anaemia	86	5	84	–
Neutropaenia	63	46	89	62
Neutropaenic Fever	–	3	–	8
Nausea	83	11	46	–
Diarrhoea	40	3	16	0
Loss of body weight	45	0	49	3

Table 2. The results of selected clinical trials assessing the efficacy of oral vinorelbine monotherapy (standard dosing)

Author	Treatment line	Patients number	Drugs	ORR (%)	PFS (months)	OS (months)
Jassem et al. [12]	I	115	VRB p.o. vs. VRB i.v.	14 vs. 12	3.2 vs. 2.1	9.3 vs. 7.9
Chen et al. [13]*	I	117	VRB vs. ERL	8.9 vs. 22.8	2.53 vs. 4.57	9.3 vs. 11.67 (p = 0.6957)
Camerini et al. [14]*	I	43	VRB	18.6	4.0	8.0
Gridelli et al. [15]*	I	56	VRB	11.0	3.7	8.2
Kanard et al. [16]*	I	58	VRB	3.4	3.5	7.5
Hirsch et al. [17]	I	189	VRB p.o. vs. VRB i.v.	4 vs. 13	3.8 vs. 5.5	6.0 vs. 9.0
Kosmidis et al. [18]*	I	74	VRB vs. PXL	6 vs. 13	2.1 vs. 2.6	3.1 vs. 5.1 (p = 0.95)
Rossi et al. [19]	II	20	VRB	0	2.0	4.0

*Studies including elderly patients and/or patients in moderate performance status (ECOG = 2)

VRB — vinorelbine; ERL — erlotinib; PXL — paclitaxel; ORR — objective response rate; PFS — progression-free survival; OS — overall survival

The most common adverse reactions among patients treated with oral vinorelbine were nausea and vomiting (83% and 65%, respectively), anaemia (86%) and neutropaenia (63%). In patients receiving intravenous vinorelbine the most common side effects included neutropaenia (89%), anaemia (84%), weight loss (49%), and nausea (46%).

Table 1 presents the data regarding adverse effects emerging during treatment with vinorelbine in presented trial [12].

Efficacy of oral vinorelbine monotherapy was evaluated in several other prospective phase II studies. In the majority of them the drug was used in a stable dose of 60 mg/m^2 weekly without dose escalation. The clinical trials that included elderly patients (≥ 70 years) and patients with worse performance status (PS) [2 according to the Eastern Cooperative Oncology Group (ECOG) scale] should be especially highlighted, and clinical benefit was also observed in these groups of patients. The detailed presentation of all studies exceeds the publication frame. Table 2 summarises the most important results of the studies published to date in which oral vinorelbine was used in patients with advanced NSCLC.

Metronomic chemotherapy — monotherapy

Metronomic chemotherapy is based on using cytotoxic drugs with increased frequency. The oral way of administration seems to be the most convenient for the patients. The efficacy and safety of oral vinorelbine used within metronomic chemotherapy were assessed in radically treated patients with NSCLC as well as in patients with only palliative chemotherapy. A very important result was establishing the dosing schedule and maximum tolerated does (MTD).

In a phase I study conducted in 73 patients with advanced recurring solid tumours (breast cancer, NSCLC, and prostate cancer) vinorelbine was used in three different doses (30, 40, or 50 mg) administered three times a week [20]. In this study the parameters of treatment efficacy (time to treatment failure was compared between three subgroups after four and six months), adverse effects, as well as the levels of potential angiogenesis markers [fibroblast growth factor type 2 (FGF2), vascular endothelial growth factor (VEGFA), interleukin 8 — IL-8, and TSP-1] were analysed. Based on the results, the authors concluded that oral vinorelbine in the dose of 50 mg given three times a week is optimal treatment. They also determined a predictive level of FGF2 and IL-8. The most common treatment-related adverse effects were anaemia and neutropaenia [20]. In other publications assessing the safety of oral metronomic vinorelbine in patients with advances cancers the dose of 50 mg was also recognised as optimal [9, 21].

Table 3. The results of phase II clinical trials in patients with advanced NSCLC receiving monotherapy with oral metronomic vinorelbine

Author	Patients number	Mean age	PS = 2 (%)	ORR%	PFS	OS
Camerini et al. [22]	43	80	62	19	5	9
Kontopodis et al. [23]	46	65	19	11	2.2	9.4

PS — performance status; ORR — objective response rate; PFS — progression-free survival; OS — overall survival

Table 4. Adverse effects during monotherapy with oral metronomic vinorelbine in patients with advanced NSCLC based on the results of published phase II studies

	Total (%)		Grade 3–4 (%)	
	Camerini et al. [22]	Kontopodis et al. [23]	Camerini et al. [22]	Kontopodis et al. [23]
Anaemia	44	58.6	0.1	4.3
Neutropaenia	4	28	0.1	24
Fatigue	32	54.4	0.1	10.9
Diarrhoea	10	8.7	0.1	2.2
Nausea	8	13.0	0	2.2
Vomiting	5	15.2	0	4.3

Based on the results of presented trials a phase II clinical study was designed in patients with advanced NSCLC, who received in a first line systemic treatment a recommended dose of oral vinorelbine [22]. The analysis included a group of 43 patients at the age of ≥ 70 years with cancer in stage IIIB or IV and in good or moderate PS (ECOG 0–2). Patients were treated until disease progression or unacceptable toxicity was documented. Objective response rate (ORR) and safety were assessed as well as quality of life (QoL) and in some of the patients VEGF and TSP1 level. In the analysed group ORR was 19%. Nearly 60% of patients had clinical benefit during treatment (disease control lasting at least 12 weeks since treatment initiation). Median PFS was five months and median OS was nine months; 37% of the patients were still during follow-up after one year. The most common adverse effects during treatment was anaemia (44%), fatigue (32%), and diarrhoea (10%). Table 3 presents the detailed data. No negative influence on QoL was observed, defined by results obtained in the *Functional Assessment Cancer Therapy — Lung* (FACT-L) questionnaire. A higher level of VEGF before treatment initiation was a predictive factor of response to metronomic vinorelbine [22].

The authors of another publication analysed the efficacy and safety of oral metronomic vinorelbine used in second and further lines of palliative chemotherapy [23]. Response and survival rates as well as safety profile were assessed in a group of 46 patients. In general, ORR was noted in 11% of patients and another 20% of patients showed disease stabilisation. Median PFS and OS were 2.2 and 9.4 months, respectively; 30% of the patients were still undergoing observation after one year. The most common adverse effects during treatment were anaemia (58%) and neutropenia (28%), which in 11% of cases were complicated by neutropaenic fever. The most common non-haematological toxicity was fatigue (54%). Table 4 presents the detailed data.

Metronomic chemotherapy — doublet protocols

Recently the results of clinical trials conducted in population of patients with advanced NSCLC were also published, in which oral metronomic vinorelbine was used in combination with other anticancer drugs [24, 25]. The first study analysed the efficacy of metronomic vinorelbine combined with sorafenib [24]. The study design divided the total group of 46 patients into three cohorts, depending on vinorelbine dose (60, 90, or 120 mg weekly, respectively). Additionally, the sorafenib dose was escalated depending on treatment tolerance. Initial sorafenib dose was 200 mg twice daily and maximum dose was 800 mg twice daily. Therapeutic responses, survival parameters, safety profile, and predictive level of angiogenesis markers (among others TSP-1 and circulating endothelial cells) were assessed. Furthermore, changes in tumour vasculature were analysed using dynamic, contrast-enhanced magnetic resonance (DCE-MR). The rate of ORR in the whole analysed population was 9%, and 65% showed clinical benefit. Median PFS and OS were 4.4 and 8.2 months, respectively. Small sample size and different doses of

assessing drugs makes conclusions regarding optimal treatment and unequivocal safety profile very difficult. Multivariable analysis indicated independent predictive levels of biomarkers (number of circulating endothelial cells, DCE-MRI parameters) [24].

Another prospective phase II clinical trial assessed vinorelbine given in the dose of 60 mg three times in week combined with cisplatin in a standard dose of 80 mg/m^2 every 21 days [25]. The study included 41 patients with advanced NSCLC in good PS. Thirty-seven percent of patients obtained partial responses and another 28% of patients had a disease stabilisation. Median PFS was 4.2 months, and median OS was 12 months. Fifty-two% of the patients were still undergoing observation after one year. The majority of patients experienced haematological toxicities (anaemia — 85%, leukopaenia — 40%, neutropaenia — 54%). Three patients had a neutropaenic febrile during treatment as a complication [25].

There is another study currently ongoing, aiming to assess the efficacy of metronomic vinorelbine in combination with bevacizumab (NCT00755170). In other trial the clinical value of metronomic vinorelbine will be analysed in patients with advanced NSCLC after platinum-based chemotherapy (NCT02176369) [26].

Summary

Recent years have brought new evidence regarding metronomic chemotherapy. It is already known that the immunomodulatory effect plays an important role, together with antiangiogenic activity. The highest number of publications concerns metronomic use of cyclophosphamide and vinorelbine (agents that have already been used for many years in standard doses). Vinorelbine is a drug of potential clinical value in NSCLC patients. Already published data indicate a very good safety profile, particularly in NSCLC patients in good and moderate PS receiving vinorelbine in first-line treatment [22]. However, it should be underlined that to date there have been no results of a phase III clinical study aimed at comparing the efficacy and safety of vinorelbine given in standard dosing schedules with metronomic vinorelbine in NSCLC patients. It is important to assess the subgroup of patients who could benefit from metronomic chemotherapy the most. Authors publishing in this field suggest that metronomic chemotherapy should be considered in elderly patients with contraindications to platinum-based doublet chemotherapy. Metronomic chemotherapy could be also a therapeutic option for patients previously treated with palliative chemotherapy [23].

Metronomic chemotherapy is not a standard care in NSCLC patients. Prospective randomised clinical trials should be conducted, the results of which could allow the determination of actual clinical benefit. One of the important elements should be prospective analysis of QoL in patients treated with metronomic chemotherapy, which should in principle be used continuously up to disease progression. Identification of predictive factors in reference to antiangiogenic effectiveness of this therapy is another point of interest, together with analysis of the efficacy of metronomic chemotherapy combined with immunomodulatory and antiangiogenic drugs.

References

1. Reck M, Popat S, Reinmuth N et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Annals of Oncology 2014; 25: 27–39.
2. Andre N, Carre M, Pasquier E. Metronomics: towards personalized chemotherapy? Nat Rev Clin Oncol 2014; 11: 413–431.
3. Browder T, Butterfield C, Kraling B et al. Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer. Cancer Res 2000; 60: 1878–1886.
4. Hanahan D, Bergers G, Bergsland E. Less is more, regularly metronomic dosing of cytotoxic drugs can target tumor angiogenesis in mice. J Clin Invest 2000; 105: 1045–1047.
5. Gnoni A, Silvestris N, Licchetta A et al. Metronomic chemotherapy from rationale to clinical studies: a dream or reality? Clin Rev Oncol 2015; 95: 46–61.
6. Mavreoeidis L, Sheldon H, Briasoulis E et al. Metronomic vinorelbine: anti-angiogenic activity in vitro in normoxic and severe hypoxic conditions, and severe hypoxia-induced resistance to its anti-proliferative effect with reversal by Akt inhibition. Int J Oncol. 2015; 47: 455–464.
7. Wierzbowska A, Krawczyńska A, Wrzesień-Kuś A, Sobczak-Pluta A, Robak T. Trombospondyna-1 i jej znaczenie w biologii nowotworów układu krwiotwórczego. Acta Haemtol Pol 2004; 35: 15–26.
8. http://www.leki-informacje.pl/sites/default/files/chpl_vinorelbinestrides_0.pdf
9. Briasoulis E, Pappas P, Puozzo C et al. Dose-ranging study of metronomic oral vinorelbine in patients in patients with advanced refractory cancer. Clin Cancer Res 2009; 15: 6454–6461.
10. http://file.esculap.com/pl/20080613_navelbine_kaps_chpl.pdf
11. Krzakowski M, Lucas C, Gridelli C. Fractionated scheme of oral vinorelbine as single-agent therapy or in combination with cisplatin concomitantly with thoracic radiotherapy in stage III non-small cell lung cancer: dose escalation phase I trial. Clinical Lung Cancer 2014; 15: 266–273.
12. Jassem J, Ramlau R, Karnicka-Młodkowska H et al. A multicenter randomized phase II study of oral vs. intravenous vinorelbine in advanced non-small-cell lung cancer patients. Annals of Oncology 2001: 12; 1375–1381.
13. Chen YM, Tsai CM, Fan WC et al. Phase II randomized trial of erlotinib or vinorelbine in chemo naive, advanced, non-small cell lung cancer patients aged 70 Years or older. J Thorac Oncol 2012; 7: 412–418.
14. Camerini A, Valsuani C, Mazzoni F et al. Phase II trial of single-agent oral vinorelbine in elderly (> 70 years) patients with advanced non-small-cell lung cancer and poor performance status. Annals of Oncology 2010; 21: 1290–1295.
15. Gridelli C, Manegold C, Mali P et al. Oral vinorelbine given as monotherapy to advanced, elderly NSCLC patients: a multicenter phase II trial. Eur J Cancer 2004; 40: 2424–2431.
16. Kanard A, Jatoi A, Castillo R, Geyer S, Schulz T. Oral vinorelbine for the treatment of metastatic non-small cell lung cancer in elderly patients: a phase II trial of efficacy and toxicity. Lung Cancer 2004; 43: 345–353.
17. Hirsh V, Desjardins P, Needles B et al. Oral versus intravenous administration of vinorelbine as a single agent for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC): a randomized phase II trial. Am J Clin Oncol 2007; 30: 245–251.
18. Kosmidis P, Syrigos K, Kalofonos H et al. Vinorelbine versus paclitaxel for patients with advanced non-small cell lung cancer and performance status of 2. Anticancer Res 2012; 32: 175–181.
19. Rossi D, Catalano V, Alessandroni P, Fedeli A, Fedeli S. A phase II study of single-agent oral vinorelbine in patients with pretreated advanced non-small-cell lung cancer. Clin Lung Cancer 2007; 8: 382–385.

20. Briasoulis E, Aravantinos G, Kouvatseas G 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.
21. Rajdev L, Negassa A, Dai Q et al. Phase I trial of metronomic oral vinorelbine in patients with advanced cancer. Cancer Chemother Pharmacol 2011; 68: 1119–1124.
22. Camerini A, Puccetti C, Donati S et al. Metronomic oral vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer: results of phase II trial (MOVE trial). BMC Cancer 2015; 15: 359.
23. Kontopodis E, Hatzidaki D, Vartalitis I 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 Chomother 2013; 25: 49–55.
24. Tan E, Tan D, Li W, Haalan B, Ang M. Metronomic vinorelbine (oral) in combination with sorafenib in advanced non-small cell lung cancer. Lung Cancer 2015; 88: 289–296.
25. Katsaounis P, Kotsakis A, Agelaki S 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: 821–827.
26. https://clinicaltrials.gov/