# Dose-Ranging Study of Metronomic Oral Vinorelbine in Patients with Advanced Refractory Cancer

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**Abstract**

**Aim:** To determine the safe dose range and pharmacokinetics of metronomic oral vinorelbine and obtain preliminary data on biomarkers and efficacy in patients with advanced cancer.

**Methods:** Successive cohorts of patients received escalated doses of oral vinorelbine given thrice a week until disease progression, unacceptable toxicity (UT), or consent withdrawal. UT was any grade 4 toxicity, or grade 2 or 3 toxicity that would result to longer than 2-week break during the first 2 months of treatment. Blood samples were collected for pharmacokinetics and quantification of angiogenesis regulatory proteins.

**Results:** Sixty-two patients (median age, 60 years) enrolled at six dose levels from 20 to 70 mg and received treatment for median 12.25 weeks (range, 2-216+). Unacceptable toxicity occurred in two of six patients treated at 60 mg (leucopenia grade 4 and epistaxis grade 2) and in one at 70 mg (leucopenia grade 2). The upper metronomic dose was 50 mg. Objective antitumor response documented in eight cases and 32% of patients experienced disease stability for minimum 6 months. Three responders (renal cancer, medullary thyroid carcinoma, and Kaposi sarcoma) received nonstop treatment for over 3 years without overt toxicity. Low pretreatment levels of circulating interleukin-8, vascular endothelial growth factor, and basic fibroblast growth factor were found predictors of efficacy. Steady-state concentrations of vinorelbine and its active metabolite ranged from 0.5 to 1.5 ng/mL.

**Conclusions:** Metronomic administration of oral vinorelbine is feasible at doses up to 50 mg thrice a week and can yield sustainable antitumor activity without overt toxicity, probably through antiangiogenic mechanism. Further clinical investigation is warranted. (Clin Cancer Res 2009;15(20):6454–61)

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Anticancer chemotherapy is typically administered in cycles of maximum tolerated doses (MTD) on the intent to potentially maximize the therapeutic outcome (1, 2). However, conventional and even intensified and megadose chemotherapy practices have brought only modest survival benefits in patients with most common metastatic cancers, and yet at the cost of quality-of-life compromising side effects (3–5).

In the antipode of maximum tolerated dose chemotherapy stands metronomic chemotherapy (MC). This is a novel dosing strategy that refers to dense, nonbreak administration of subtoxic doses of chemotherapy over protracted periods of time, even years, with the aim to primarily target tumor angiogenesis (6–8). MC is by concept an endothelial cell–targeted antiangiogenic therapy, which exploits the high turnover rate and remarkable sensitivity of endothelial cells to cytotoxic agents to which, by virtue of blood circulation, they are directly exposed (9, 10).

MC moved fast to clinical investigation on the basis of robust preclinical data (11, 12). Nevertheless, early clinical development of MC has been empirical and identification of optimal dosing and agents have yet to be established (13).

## Translational Relevance

Metronomic chemotherapy is a novel dosing strategy that refers to dense, nonbreak administration of subtoxic doses of chemotherapy over protracted periods of time, even years, with the aim to primarily target tumor endothelial cells. Metronomic chemotherapy moved fast to clinical investigation on the basis of robust preclinical data, but early clinical development has been empirical. This is the first-in-man dose-investigating study of metronomic chemotherapy with an antimicrotubule agent. In addition, this study provides clinical proofs supporting the concept of antiangiogenic basis of metronomic chemotherapy. The demonstrated sustainable antitumor activity and negligible toxicity of this therapy, taken together with the pharmacokinetic and biomarker data, suggest that this is a novel therapeutic approach, which opens new horizons in cancer antivascular therapy beyond vascular endothelial growth factor blockade.

Among classes of cytotoxic drugs, antimitotics are thought to be the most proper for metronomic use because of their potency to suppress microtubule dynamics and interfere with endothelial cell functionality at very low concentrations (14, 15). We selected for metronomic investigation vinorelbine, a semisynthetic *Vinca* alkaloid with antimicrotubule activity, because of its availability in oral formulation (Navelbine soft caps). Oral administration is clearly advantageous when considering chronic metronomic administration (7, 16).

Oral vinorelbine (VRL) has shown bioavailability of 40%, which is practically not influenced by food or age, moderate interpatient variability, and linear pharmacokinetics (17–20). Its metabolism has been elucidated and only 4-O-deacetylvinorelbine (DVRL) has been found active (21–24). Both VRL and DVRL are mostly eliminated via the bile, and only limited amounts are excreted in urine (20, 25). The elimination half-life of VRL is ~40 hours and 168 hours for DVRL (20, 25, 26).

Given that optimal metronomic dose could theoretically be anyone in a safe dose range (27), we designed a two-stage investigation approach: first to establish a safe dose range and second to identify the optimal metronomic dose (NCT00278070). In this article, we report the results on safety, tolerability, pharmacokinetics, biomarkers, and activity of ascending doses of metronomic VRL in patients with advanced refractory cancer. To our knowledge, this is the first dose investigating clinical trial of MC.

## Patients and Methods

***Study design and objectives.*** This was an open-label, ascending-dose trial, conducted by two Academic Units, the Medical Oncology departments of the Universities of Ioannina and Thessaloniki, Greece, in collaboration with the Pharmacology Department of the Medical School of the University of Ioannina and the Institute de Recherché Pierre Fabre France. The study was designed according to the current revision of the Declaration of Helsinki and was conducted in accordance with principles of good clinical practice. The study protocol was reviewed and approved by the Institutional Review Boards and Ethics Committees of the two participating centers, and written informed consent was obtained from each participant before entry into the study.

Primary objectives were to assess feasibility and safety of chronic administration of ascending doses of metronomic oral VRL (MOVIN) and determine the upper feasible metronomic dose. Secondary objectives were to characterize the toxic effects, investigate the pharmacokinetics at the different dose levels, identify circulating biomarkers of clinical relevance, and collect evidence of antitumor activity with this therapy.

***Treatment scheme and definitions.*** The dosing scheme was structured to address clinical convenience and pharmacologic issues. Considering that terminal half-life of VRL and DVRL, we selected an every-second day administration schedule, which was estimated to yield steady-state levels without drug accumulation in chronic use (28). Oral VRL (Navelbine soft caps) was received before midday lunch, thrice a week on Monday, Wednesday, and Friday. Treatment continued until disease progression, unacceptable toxicity, or on patient's decision to withdraw. A flat-fixed dosing strategy was adopted for practicality and because a somatometrically adjusting dose approach is considered insignificant in low-dose therapeutic strategies, especially whenever a biologically optimum dose is the objective (29).

Successive cohorts of patients were treated with escalated doses of oral VRL given thrice a week. The starting dose chosen was 20 mg, which was the lowest available dosage in oral formulation. Dose was escalated by 10-mg increments in successive cohorts of minimum six patients. At any dose level, at least 4 wk should pass between the entry of the first patient and recruitment continuation. Patients were followed up closely for

**Table 1.** Demograhics

| Characteristic | Value | Number | % |
|---|---|---|---|
| Patients recruited | | 62 | 100 |
| Gender (f/m( | | 30/32 | 48/52 |
| Age, y; median (range) | 60 (29-84) | | |
| Performance status | 1 (0-2) | | |
| BSA, $m^2$; median (range) | 1.7 (1.5-2.2) | | |
| Enrolled at single dose level | | 47 | 76 |
| Enrolled at multiple dose levels (intrapatient dose escalation) | | 15 | 24 |
| Two dose levels | | 11 | |
| Three dose levels | | 4 | |
| Previous therapy | | | |
| Chemotherapy | | 53 | 86 |
| Radiotherapy | | 17 | 27 |
| Hormonal therapy | | 5 | 8 |
| Prior chemotherapy regimens* | | | |
| Median number | | 2 | |
| Range | | 0-6 | |
| Tumor type | | | |
| Lung cancer | | 14 | |
| Breast cancer | | 13 | |
| Ovarian cancer | | 6 | |
| Prostate cancer | | 6 | |
| Renal cancer | | 5 | |
| CUP | | 4 | |
| Sarcoma | | 4 | |
| Mesothelioma | | 2 | |
| Other† | | 8 | |

Abbreviations: BSA, body surface area; f, female; m, male; CUP, cancer of unknown primary site.
*Lung cancer and ovarian cancer patients had been previously treated with carboplatin-based combination chemotherapy, and breast cancer patients had received taxane-anthracycline combinations. No one patient had previously received VRL.
†Bladder, colorectal, head-neck, melanoma, neuroendocrine, thyroid, cervical cancer, and Hodgkin's Lymphoma.

**Table 2.** Treatment and toxicity

| Dose level | Dose mg (Mo-We-Fr) | Pts treated | BSA median (range) | Weeks on treatment* median (range) | Total treatment weeks | Non-UT adverse events (G1-2) registered during study | | | UT events (time of event) | Patients with any adverse event (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Anemia | WBC | Nonhematologic | | |
| 1 | 20 | 16 | 1.70 (1.60-2.2) | 12 (5-41) | 254 | 0 | 0 | 3 | | 3 (19%) |
| 2 | 30 | 18 | 1.75 (1.50-1.9) | 14 (4-216+) | 526 | 2 | 0 | 4 | | 6 (33%) |
| 3 | 40 | 26 | 1.90 (1.50-2.0) | 14 (3-212+) | 636 | 0 | 1 | 5 | | 5 (19%) |
| 4 | 50 | 13 | 1.84 (1.70-2.0) | 9 (2-202) | 313 | 1 | 0 | 2 | | 3 (23%) |
| 5 | 60 | 6 | 1.93 (1.80-2.3) | 11,5 (8-54) | 110 | 0 | 0 | 0 | Epistaxis G2 (wk 9); ANC G4 (wk 12) | 2 (33%) |
| 6 | 70 | 2 | 1.85 (1.70-2.0) | 12,5 (8-17) | 25 | 0 | 1 | 1 | ANC G2 (wk 7) | 2 (100%) |
| Totals | | 81 | | | 1,864 | | | | | 22 (27%) |

Abbreviations: Pts, patients; UT, unacceptable toxicity; (+), ongoing; G, toxicity grade.
*The treatment duration in cases of intrapatient dose escalation (n = 15) was censored at the time point of dose escalation.

toxicity and adverse events were recorded according to National Cancer Institute Common Toxicity Criteria for Adverse Events version 3. Unacceptable toxicity was considered any grade 4 toxicity or grade 2 or 3 toxicity that would result to treatment discontinuation for >2 wk during the first 2 mo of treatment. Dose escalation was allowed if no more than one of six patients treated at any dose level experienced grade 2 and higher toxicity, except alopecia or inadequately treated vomiting. To facilitate a most reliable characterization of toxicity, larger patient-cohorts per dose level were sought at critical dose levels at which biological activity were first seen. Intrapatient dose escalation was acceptable in this trial on the intent to avoid exposing many patients to subtherapeutic doses. Patients who had neither obtained objective response nor experienced any grade 2 or higher toxicity after an 8-wk treatment were offered the option to register at the next dose level. Dose escalation would end up whenever a minimum of two patients developed unacceptable toxicity at a given dose level, which would define the roof-dose level. One level below the roof-dose level would be the upper metronomic dose. Prophylactic antiemetics were allowed on demand. Patients with measurable disease were assessed for response by the Response Evaluation Criteria in Solid Tumors method (30).

***Patients.*** This clinical trial recruited patients with histologically confirmed advanced or metastatic tumors who had progressed despite standard treatments or lacked standard treatment options, and the following criteria: age above 18 y, WHO performance status worst of 2, hemoglobin of 10 g/dL, WBC of 3 × 10^9/l, absolute neutrophil count (ANC) of 1.5 × 10^9/l, platelets of 150 × 10^9/l, bilirubin of <1.5× upper limit of normal, transaminases of 2.5× upper limit of normal, creatinine of 1.5× upper limit of normal, and a time interval longer than 4 wk following any surgery except for biopsy, previous irradiation, or chemotherapy. Eligible candidates were required to provide a signed informed consent for participation and donation of biological material for research purposes, before registration.

***Follow-up and sampling.*** Patients attended clinics every 2 wk for the first 2 mo and monthly thereafter, for clinical assessment and blood sampling. They would exit the trial for disease progression, toxicity, or on their own wish. Blood samples of 5 mL were collected into EDTA tubes and in gel-coated serum tubes before treatment initiation and at follow-up visits before administration of VRL. Samples were banked at -20°C freezer until analysis.

***Biomarkers assessment.*** Serum concentrations of basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF)-A, interleukin-8 (IL-8), and thrombospondin-1 (TSP1) were determined using commercially available quantitative sandwich enzyme immunoassays. Quantikine kits (R&D Systems, Inc.) were used for bFGF, VEGF, VEGFr2, and IL-8, and ChemiKine Human TSP1 EIA kit for TSP1 (Chemicon International, Inc.). Protocols, procedures, and equipment were used according to the manufacturer's specifications. Optical densities were determined using a microfilter plate reader (DAS-A3) with filters for 450 nm (IL-8, VEGF, VEGFr2) and 490 nm (bFGF, TSP1). All analysis was carried out in duplicate.

***Pharmacokinetic analysis.*** Whole blood samples were shipped on dry ice to the Institute de Recherche Pierre Fabre, Castres, France, where they were analyzed. Concentrations of VRL and its main metabolite, DVRL, were quantified using a sensitive liquid chromatography tandem mass spectrometry method previously reported (31). Briefly, the method consisted in deproteinization of blood samples with a mixture of ethanol and acetonitrile followed by a liquid chromatography coupled through an electrospray interface to a tandem mass spectrometry in positive mode detection. Concentration data collected during a bioavailability study conducted on patients receiving 80 mg/m$^2$ oral Navelbine (19) were dose-adjusted and used for steady-state profiles simulation (WinNonlin V5, Pharsight). A mean profile was drawn from mean concentration values and a lower profile was simulated from the patient with the lowest concentrations. Observed data from the current study were plotted on those profiles after dose-adjustment to a same dose (60 mg).

***Statistics.*** Statistical analysis was applied to investigate the effects of different doses on the WBC and ANC, and the biomarkers predictive power. Mixed effects models with intercept as random effect and compound symmetry variance-covariance matrix were used to investigate difference in the mean WBC and ANC between dose levels and across time (32). To preserve the models' ability to best-fit data patterns, we included data for up to 24 wk to derive estimates on maximum possible observations.

Biomarkers' predictive power (objective responders plus SD, ≥6 mo) was assessed using ROC curves analysis (33). A composite biomarker using the joint predictive power of all the markers was also constructed using logistic regression. A Mann-Whitney test as described by DeLong et al. (34) was used to test for statistically significant differences of the area under the ROC curves between each of the biomarkers and the composite model. An ANOVA analysis was further used to investigate differences in means between controls and each response status.

Statistical analysis was done using the SAS v9.1.3 statistical package (SAS Institute, Inc.). All reported *P* values are two sided and results were considered significant at $\alpha = 0.05$.

## Results

***General outcomes.*** Sixty-two patients were enrolled between June 2004 and February 2006 and were treated at six dose levels (Table 1). Forty-seven patients were treated at single dose level,

11 patients at two dose-levels, and 4 patients at three consecutive dose levels. Overall, 81 subjects were treated at six dose levels from 20 to 70 mg. The overall dose escalation scheme, number of patients treated per dose level, and treatment duration are listed in Table 2. The median duration of treatment administered per patient was 12.25 weeks (range, 2-216+ weeks). At last follow-up (January 2009), two patients remained on treatment at 30 and 40 mg, respectively, for ~4 years.

***Toxicity.*** All subjects treated at the six dose levels were assessed for toxicity, irrespective of intrapatient escalations. Clinically relevant suppression of blood counts was rare and was only noted at the highest two dose levels. Unacceptable toxicity occurred in two patients at 60 mg (leucopenia grade 4 on treatment week 14 and epistaxis on week 9) and in one patient at 70 mg (leucopenia grade 2 on week 7). The distributions of toxicities as a function of dose are shown in Table 2. Upper metronomic dose of oral VRL at this dosing schedule was the 50 mg. Clinically relevant nonhematologic toxicities were practically absent in the tested dose spectrum. The main nonhematologic toxicity was diarrhea grade 1, which occurred occasionally on the day of treatment in a few patients. Moreover, mild manageable hypertension occurred in one patient. Peripheral neuropathy was practically absent; even patients treated nonstop for >3 years. The absence of cumulative neurotoxicity was documented electrophysiologically. Vomiting and nausea were also negligible and antiemetics were not required in the majority of patients.

Based on the mixed effects models analysis, a statistically significant difference in the mean values of WBC between dose levels was detected ($P$ = 0.023) but not across time ($P$ = 0.583; Fig. 1A presents model fit for the dose of 40 mg). With respect to the dose of 20 mg, the doses of 30, 40, and 60 mg had an average difference of -747 cell number/μL ($P$ = 0.070), -688.2 cell number/μL ($P$ = 0.077) and -1861.6 cell number/μL ($P$ = 0.003; The dose levels of 50 and 70 mg were excluded from this analysis due to insufficient for the model number of observations across time, whereas and at dose of 60 mg, the patient with unacceptable toxicity was also excluded due to the extremity of the observed value). With regard to ANC, there was no statistically significant difference between dose levels or across time ($P$ = 0.136 and $P$ = 0.784, respectively; Fig. 1B presents model fit for the dose of 40 mg).

***Antitumor activity.*** Sustained tumor remission was documented in 8 among 52 patients who had measurable disease by imaging studies or elevated serum prostate-specific antigen in case of prostate cancer. (Supplementary Table S1; Supplementary Fig. S1; Fig. 2A–C). Responded patients had renal carcinoma (1), hormone-refractory prostate cancer (3), diffuse large B-cell lymphoma (1), ovarian cancer (1), medullary thyroid carcinoma (1), and Kaposi sarcoma (1). Responses were seen within 2 to 3 months from start of treatment and lasted from 13 to 48+ months; toxicity was never a problem in these cases. In addition, 32% of patients experienced disease stability at minimum 6 months. Illustration of selected responded cases is given below.

***Illustration of objective response cases.*** A 56-year-old man, with dyspnea due to multiple lung metastases from renal cell carcinoma, entered onto the trial in January 2005 at 50 mg dose level. The patient experienced fast relief of dyspnea and partial remission of the lung metastases was documented. One year later, he had his residual pulmonary masses resected and pathology assessment showed significant decrease of microvessel density and increased expression of endogenous angiosuppressing protein TSP1 in resected metastases compared with the primary tumor (Fig. 2A). This single kidney patient continued treatment uneventfully for >3 years. Another 71-year-old man with Kaposi sarcoma achieved sustained remission of his disease with MOVIN 40 mg, which continues for almost 4 years (Fig. 2B). A third, 68-year-old man, with diffuse large B-cell lymphoma refractory to two prior combination chemotherapy regimens plus rituximab had partial response on MOVIN 60 mg, which lasted for 14 months (Fig. 2C).

***Biomarkers.*** Baseline pretreatment levels of bFGF, IL-8, and VEGF formulated an uphill continuum from the normal controls to nonresponders with statistically significant difference. In the opposite, the levels of endogenous antiangiogenic protein TSP1 were highest in the control group and lowest in nonresponders, yet not statistically significant (data not shown).

Using ROC curves, we were able to estimate the predictive power for response of each biomarker (Fig. 3). In terms of the area under the curve value, TSP1 had the smallest value 59% [95% CI (95% confidence interval), 35-83%] followed

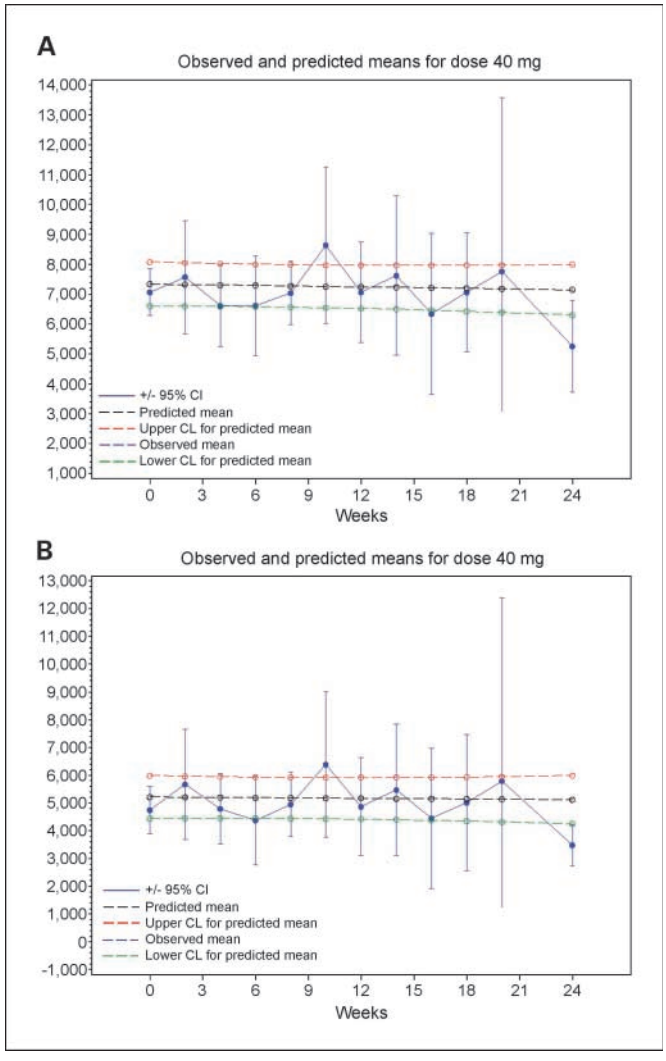


**Fig. 1.** Mixed effects model fit for the dose of 40 mg for WBC (*A*) and ANC (*B*).

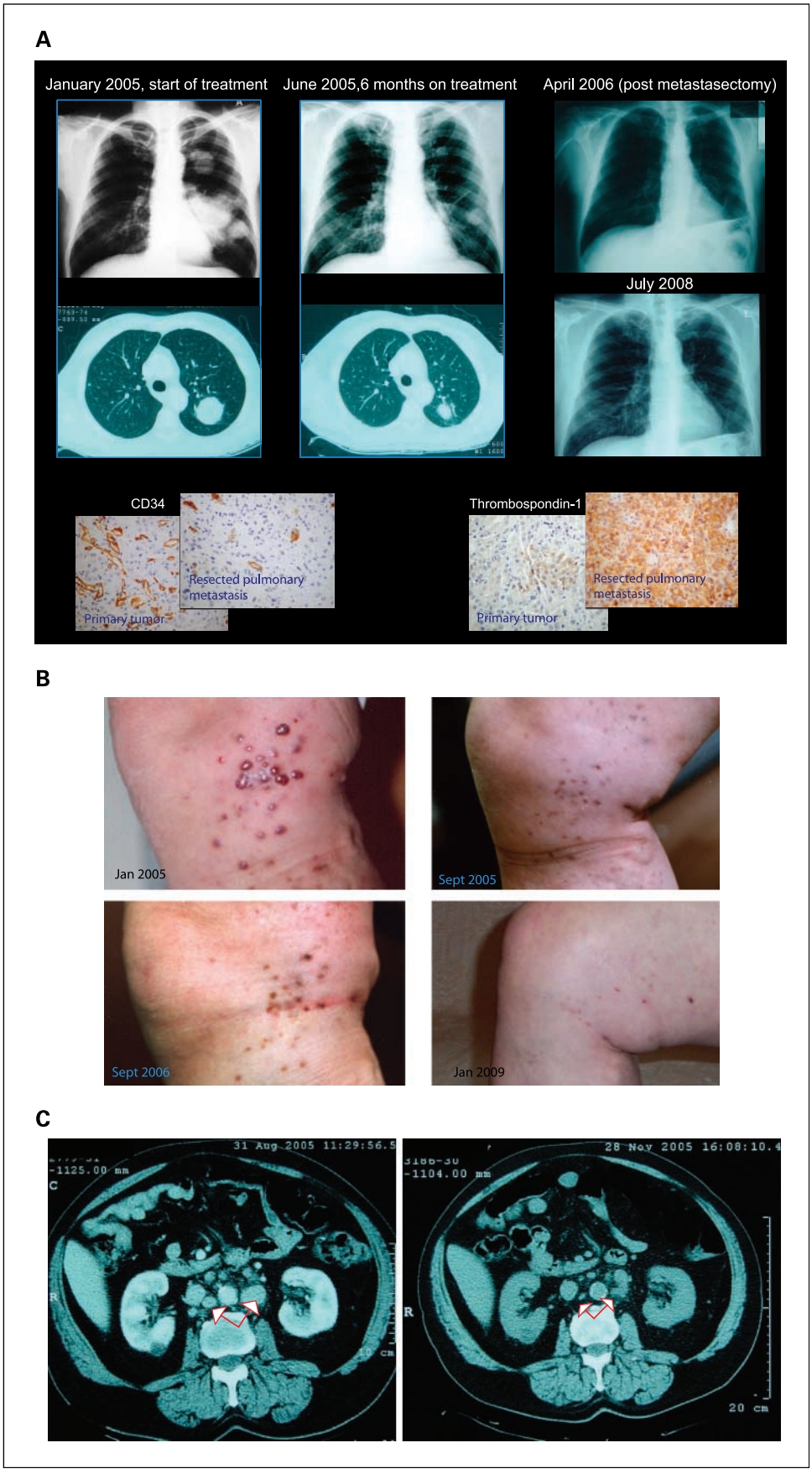


**Fig. 2.** Objective responses in patients treated with MOVIN. *A,* partial remission of renal cancer pulmonary metastases in a patient treated with MOVIN at 50 mg. The regressed lesions were surgically resected and assessed pathologically for angiogenesis. *Bottom,* immunohistochemistry of biopsy sections show decreased microvessel density (CD34) and increased expression of TSP1 in the resected metastatic lesions. *B,* durable partial remission of Kaposi sarcoma in a 71-y-old male patient treated with MOVIN 40 mg. He is on nonbreak treatment for 44 mo now. *C,* partial remission of a refractory non–Hodgkin lymphoma treated with MOVIN 60 mg in a 68-y-old male patient who had failed to two lines of chemotherapy.

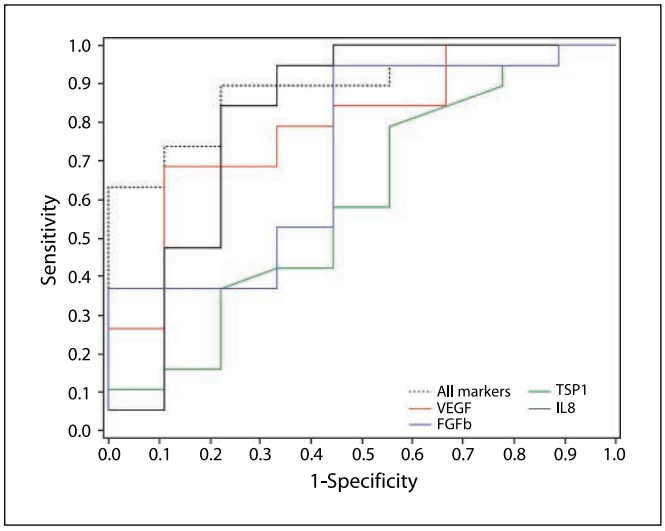


**Fig. 3.** ROC Curves for the biomarkers' ability to predict response.

by bFGF with 71% (95% CI, 49-93%), VEGF with 79% (95% CI, 61-97%), and IL-8 with 81% (95% CI, 55-100%). We devised a model using logistic regression that provided the joined predictive ability of all the biomarkers. The area under the curve for the joined model was 89% (95% CI, 75-100%). Overall, there was statistically significant difference between the curves ($P < 0.0001$). We also investigated by using general linear model analysis if the effect of the biomarkers on response was affected by the presence of the dose indicator, but the sample size was not large enough to allow with sufficient accuracy the estimation a possible relationship.

***Pharmacokinetic analysis.*** From the patients included in this study, 37 (60%) individuals with minimum two serial blood samples had a pharmacokinetic evaluation. The number of data per patient varied from 2 to 7 and represented a total of 130 collected blood samples. All sampled patients but three who had a dose increase 3 to 6 months after the start of treatment received a fixed dose.

Blood samples were mostly collected between 14 and 150 days after the start of treatment and up to 1 year in one patient. Dose proportional increase of exposure is strongly suggested from direct plot (Fig. 4A) and better illustrated on the ratio (concentration/dose), which must be constant when pharmacokinetics is linear (Fig. 4B). The observed range of variability is the consequence of the fixed dosing administered whatever the patient's body surface area.

The steady-state of blood concentrations for both VRL and DVRL was achieved from day 14 and was stable over the 5 months of assessment and ranged from 0.5 to 1.5 ng/mL (Supplementary Figs. S2 and S3). The profiles of observed concentrations were in agreement with those simulated using a body surface area of 1.7 $m^2$ and the dose-adjusted data from a previous study performed at usual dose level (80 $mg/m^2$; ref. 19).

## Discussion

The MOVIN trial provide clinical proofs, which support the concept of the antiangiogenic basis of MC (8). These data are confirmatory and complementary to already published metronomic studies with other drugs (11, 35).

A major finding in this study was the negligible toxicity of MOVIN therapy. Although side effects of this therapy were anticipated to be mild, the striking absence of clinically significant toxicity with prolonged administration of effective doses of metronomic VRL is surprising (36). Cancer angiogenesis attracted strong research interests that led to successful development of therapeutics targeting the VEGF- VEGFR2 pathway of endothelial cells (37). By intervening with the VEGF pathway, targeted drugs can also affect homeostasis of physiologic endothelial cells, associated with characteristic toxicities such as edema, hypertension, and fatigue (38). Such toxicities were practically absent in the defined safe dose range of metronomic VRL. This favorable toxicity profile of this therapy if confirmed in more studies might allow MOVIN therapy to claim superiority in terms of safety against other targeted antiangiogenic therapeutics in future randomized trials.

The current dosing administration schedule was designed on the basis of feasibility and pharmacokinetic considerations. The strength of VRL capsules was 20 and 30 mg. A daily schedule would not have enabled to assess the 10 mg/day dose level, whereas this would have been possible when using a 20 mg every second day. Finally for practical reasons, a three-time administrations per week was selected. More than half (60%) of patients allowed collecting blood samples. The pharmacokinetic data illustrated a very reproducible exposure among the treatment period. Most of the pharmacokinetic blood samples were collected from 2 weeks up to 5 months after the start of treatment and, therefore, really reflect the steady-state of blood exposure for both VRL and DVRL. A more frequent pharmacokinetic evaluation might probably have predicted more accurately

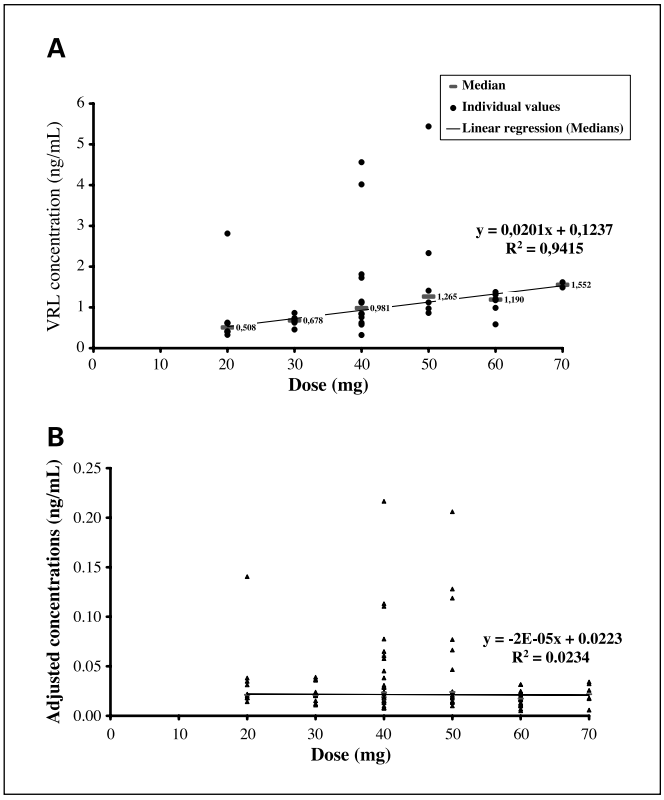


**Fig. 4.** VRL steady-state blood concentrations versus dose levels (37 patients, 130 samples). *A*, raw data; *B*, dose-adjusted data.

the PK of MOVIN. However, achievement of steady-state concentrations over long periods of treatment and dose linearity were adequately shown. The linearity of oral VRL pharmacokinetics already shown in the range 60 to 100 mg/m$^2$ is now confirmed in the lower range of doses (24, 26). Low blood concentrations of VRL and DVRL fitted well with the simulated profiles achieved from a previous study and illustrated a continuous and stable exposure to both VRL and DVRL throughout the treatment (19). Achieved in this trial, steady-state concentrations were found *in vitro* to optimally inhibit proliferation of endothelial cell and induce expression anti-angiogenic molecular effects of endothelial cells (39). These data support that the chosen schedule of oral VRL serves well the concept of metronomic therapy, which by definition requires protracted exposure of endothelial cells to very low concentrations of cytotoxics (40, 41). Moreover antiangiogenic therapy is known to work optimally if endothelial cells are exposed to steady levels of inhibitors (42).

Antitumor activity of low-dose and MC has already been reported in several types of cancers (12). In this trial, MOVIN administered at doses from 20 to 50 mg generated some remarkably long-lasting tumor responses against various cancers. Interestingly, patients who benefited from this therapy tended to have low levels of endogenous angiogenesis promoters (IL-8, bFGF, and VEGF) and high levels of the endogenous angiogenesis inhibitor TSP1. These are encouraging preliminary data in view of unmet need for validated biomarkers of angiogenesis cancer antiangiogenic therapies (43, 44). Other investigators have found that baseline circulating endothelial cells correlate significantly with response and outcome in patients treated with MC (12). Probably both circulating endothelial cell– and circulating angiogenesis–regulating proteins should be considered for patient selection in future trials of cancer antivascular therapies.

In conclusion, chronic administration of MOVIN, given thrice a week, is feasible at doses up to 50 mg. The sustainable antitumor activity and negligible toxicity of this therapy, taken together with the pharmacokinetic and preliminary biomarker data, suggest that this therapy is a novel angiogenesis-targeted therapy beyond VEGF blockade, which merits further clinical investigation. We propose that the full therapeutic potential of MOVIN should be explored through randomized clinical trials that would entail combinations with conventional chemotherapy and other antiangiogenic agents as others have also suggested (45).

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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