METRO1: A Phase I Study of Metronomic Chemotherapy in Adults with Advanced Refractory Solid Tumors

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Abstract. *Background: The present monocentric and prospective phase 1 study evaluated the safety of a metronomic chemotherapy in refractory tumors. Patients and Methods: Patients with advanced solid cancer refractory to standard therapy received a combination of low-dose vinorelbine, cyclophosphamide and interferon-alpha. A dose escalation model with 3 levels was planned. The primary end-point was safety and tolerability, secondary end-points were treatment continuation rate at 4 months, progression-free survival (PFS), overall survival (OS), radiological assessment (MRI) of anti-angiogenic effect. Results: Thirty patients were enrolled. No dose-limiting toxicity was observed. All but two adverse events were toxicities of grade 1-2. Treatment continuation rate at 4 months was 6.67% (2 out of 30 patients). Median PFS and OS were 1.6 and 6.1 months. Exploratory MRI analyses related to anti-angiogenic effect did not show any relevant modification. Conclusion: This combination of metronomic chemotherapy is well-tolerated and deserves to be deeply explored in refractory solid tumors.*

Forty years ago, Judah Folkmann was a pioneer when he hypothesised the existence of angiogenesis (1). Many reports from his team and others highlighted evidence of angiogenesis (2) and it has since been considered a hallmark of cancer (3). Angiogenesis is a complex process by which cancer cells interact with their microenvironment to stimulate formation of a new vasculature with the aim to be fed. This phenomenon occurs during tumor development and has been described as a necessary step for tumor growth and metastasis process so called the "angiogenic switch" (4). The major pathway identified in angiogenesis has been the VEGF (vascular epithelial growth factor) pathway (5). Three ways have been developed to inhibit angiogenesis: i) a monoclonal antibody against VEGF called bevacizumab, that has been approved for several solid malignancies such as metastatic colorectal cancer (6), metastatic lung cancer (7) and ovarian cancer (8, 9); ii) tyrosine kinase inhibitors such as sunitinib, sorafenib and pazopanib that have been approved for metastatic renal cancer (10-12); iii) a soluble receptor able to trap VEGF, called aflibercept, approved for advanced colorectal cancer (13).

Another kind of treatment not using targeted therapies has also been developed to inhibit angiogenesis: metronomic chemotherapy. This concept has been developed in the early 2000's by Hanahan and Bergsland (14). The principle of this treatment is to provide a low continuous dose of chemotherapy to obtain an anti-angiogenic effect through continuous angiogenesis inhibition. Seminal reports have shown that low continuous doses of chemotherapy were able to target angiogenesis in immunodeficient mice models (15, 16). Further studies had confirmed the anti-angiogenic effect of this therapy for resistant and refractory tumors (17-19).

We conducted a prospective phase I study (METRO-1) of dose escalation of a metronomic chemotherapy in order to study the tolerability and safety of the combination of low-dose vinorelbine, low-dose cyclophosphamide and interferon-alpha-2b.

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Key Words: Phase I, metronomic chemotherapy, angiogenesis, DCE-MRI.

Patients and Methods

Study design. This was a prospective monocentric open-label phase I dose escalation study of metronomic chemotherapy for advanced solid malignancies. The primary objective was the estimation of toxicity of the combination of continuous low-doses of vinorelbine, cyclophosphamide and interferon-alpha-2b. Secondary objectives were the estimation of the antiangiogenic effect using DEC-MRI, as well as treatment continuation rate at four months, clinical response, progression-free survival and overall survival.

Patient selection. Patients over 18 years of age or older with any advanced or metastatic solid tumor refractory to standard therapy were enrolled to the METRO-1 trial (ClinicalTrials.gov Identifier: NCT00908869). All patients provided their written informed consent. This prospective study was approved by our regional Ethics Committee. Patients should have at least one lesion measurable in dynamic contrast-enhancement (DCE)-MRI (except pulmonary lesions, adenopathy or lesion with previous radiotherapy) and should not have received chemotherapy or radiotherapy within four weeks before enrollment (six weeks with nitrosoureas and mitomycin C). All patients had a life expectancy of at least three months, Karnofsky performance status of at least 80%, absolute leukocyte count ≥3,000/mm^3, absolute neutrophil count ≥1,000/mm^3, serum creatinine ≤50 μmol/l, adequate liver function (aspartate transaminase, alanine transaminase and total bilirubin <1.5x the upper limit of normal or <2.5x the upper limit of normal if they had liver metastasis). Patients were not included if they had stable disease, history of previous malignant disease (except basal-cell or squamous-cell skin carcinomas, cervical carcinoma *in situ* or any localized tumor with at least five years of remission), a contra-indication to MRI or other study products and procedures, inclusion in another clinical trial during this study, pregnancy (or absence of contraception during genital activity), suckling and other concurrent severe or uncontrolled medical disease that could compromise participation in the trial. No prior antiangiogenic treatment was allowed. During the study, patients could not receive bisphosphonates, anticoagulant therapy and hematopoietic growth factor.

Treatment. Treatment was a combination of low-dose of oral vinorelbine (Navelbine®, Pierre Fabre Oncologie), oral cyclophosphamide (Endoxan®, Baxter) and interferon-alpha-2b (Introna®, Schering-Plough). Three levels were tested. In level 1, patients received vinorelbine 20 mg twice a week, cyclophosphamide 50 mg daily and Interferon alpha 2b 0.9×10^6 UI three times a week. In level 2, patients received vinorelbine 20 mg three times a week, cyclophosphamide 50 mg daily and interferon-alpha-2b 0.9×10^6 UI three times a week. In level 3, patients received vinorelbine 20 mg three times a week, cyclophosphamide 50 mg daily and interferon-alpha-2b 0.9×10^6 UI five times a week. In case of toxicity at level 1, a level -1 has been designed with vinorelbine 20 mg twice a week, cyclophosphamide 50 mg every two days and interferon-alpha-2b 0.9×10^6 UI three times a week. One gram of paracetamol was delivered 2 h before and 2 h after interferon administration. Treatments were delivered during 8-week cycles including six weeks of treatment and a 2-week stop. After evaluation, treatment was continued if patients displayed radiological response, stable disease or clinical benefit.

Dose escalation. The aim of escalation was to establish the dose with acceptable dose-limiting toxicity (DLT) and maximal antiangiogenic effect. After treatment of ten patients at one level, the next level was explored if there was no antiangiogenic effect or if eight patients presented a clinical progression at six weeks with no more than two patients presenting a DLT. In case of the observation of an antiangiogenic effect or with less than 8 progressive patients and no more than 2 DLTs, ten new patients were enrolled in the same dose level.

If 2/10 or 5/20 patients experienced a DLT in level 2 or 3, study was planned to be stopped and dose recommendation corresponded to the previous administered dose level. If this threshold was attained at level 1, level -1 would be explored. Levels 1 to 3 would be explored if the threshold wouldn't be reached.

Table I. *Patients' characteristics (N=30).*

Patients		N
Age	Median [range]	58.5 [35-80]
Tumor type	Breast	8 (27%)
	Urothelial	6 (20%)
	Colorectal	5 (16%)
	Surrenal	2 (7%)
	Oesophagus/Cardia	2 (7%)
	Pancreas	2 (7%)
	Melanoma	2 (7%)
	Ovary	1 (3%)
	Cervix	1 (3%)
	Liver	1 (3%)
Prior treatments	Chemotherapy	29 (97%)
	Median No. of lines [range]	2 [1-7]
	Radiotherapy	17 (57%)

Toxicity and dose adaptation. Toxicity was defined using the National Cancer Institute Common Toxicity Criteria version 3.0. Patients with grade 2 extra-haematological toxicity during one week discontinued treatment until recuperation of a grade 1 toxicity level. In case of grade 3 haematological toxicity, treatment was discontinued until return to a grade 1. DLT was defined as grade 3 or grade 4 non-haematological toxicity, grade 4 neutropenia and thrombopenia or any discontinuation for toxicity of at least fifteen days. In case of a DLT, treatment was discontinued and patient was withdrawn.

Clinical response assessment. Baseline assessments included medical history, vital signs, PS, radiological tumor measurement (RECIST 1.0), and measurement of palpable or visible lesions. Clinical evaluations were performed weekly and tumor assessments were performed every 6 weeks. Follow-up was measured from the date of treatment beginning to the date of last news for living patients. Overall survival (OS) and progression-free survival (PFS) were respectively defined as the time from treatment beginning to death from any cause or disease progression according to RECIST 1.0 criteria.

DCE-MRI. To identify an antiangiogenic effect in DCE-MRI, we compared 3 parameters (area under the curve, time to peak and slope) at the following times: baseline (in the 15 days before treatment's initiation), day 8, day 22 and day 42.

Table II. *Adverse events related according to the CTCAE v3.0 classification*.

	Level 1				Level 2				Level 3				All levels			
	Grade 1-2		Grade3-5		Grade 1-2		Grade3-5		Grade 1-2		Grade3-5		Grade 1-2		Grade3-5	
	Events	N (%)	Events	N (%)	Events	N (%)	Events	N (%)	Events	N (%)	Events	N (%)	Events	N (%)	Events	N (%)
Anemia	1	1 (10)	0	0	3	2 (20)	0	0	0	0	0	0	4	3 (10)	0	0
Asthenia	1	1 (10)	1	1 (10)	1	1 (10)	1	1 (10)	2	2 (20)	0	0	4	4 (13,3)	2	2 (6,67)
Anorexia	1	1 (10)	0	0	0	0	0	0	1	1 (10)	0	0	2	2 (6,67)	0	0
Fever	6	3 (30)	0	0	1	1 (10)	0	0	0	0	0	0	7	4 (13,3)	0	0
Shills/sweat	0	0	0	0	2	2 (20)	0	0	1	1 (10)	0	0	3	3 (10)	0	0
Abdominal pain	0	0	0	0	2	2 (20)	0	0	0	0	0	0	2	2 (6,67)	0	0
Nausea/vomiting	1	1 (10)	0	0	3	2 (20)	0	0	3	2 (20)	0	0	7	4 (13,3)	0	0
Diarrhea	0	0	0	0	0	0	0	0	1	1 (10)	0	0	1	1 (3,33)	0	0
Rectal bleeding	0	0	0	0	1	1 (10)	0	0	0	0	0	0	1	1 (3,33)	0	0
Injection site reaction	0	0	0	0	1	1 (10)	0	0	1	1 (10)	0	0	2	2 (6,67)	0	0
Chest pain	0	0	0	0	0	0	0	0	1	1 (10)	0	0	1	1 (3,33)	0	0
Dyspnea	0	0	0	0	1	1 (10)	0	0	0	0	0	0	1	1 (3,33)	0	0
Cough	0	0	0	0	0	0	0	0	1	1 (10)	0	0	1	1 (3,33)	0	0
Myalgia	3	2 (20)	0	0	1	1 (10)	0	0	0	0	0	0	4	3 (10)	0	0
Neuropathy	1	1 (10)	0	0	0	0	0	0	0	0	0	0	1	1 (3,33)	0	0
Tremor	0	0	0	0	1	1 (10)	0	0	0	0	0	0	1	1 (3,33)	0	0
Vertigo	0	0	0	0	1	1 (10)	0	0	0	0	0	0	1	1 (3,33)	0	0
Somnolence	0	0	0	0	1	1 (10)	0	0	0	0	0	0	1	1 (3,33)	0	0
Dry skin	1	1 (10)	0	0	0	0	0	0	0	0	0	0	1	1 (3,33)	0	0
Gynecomastia	0	0	0	0	0	0	0	0	1	1 (10)	0	0	1	1 (3,33)	0	0
Flush	0	0	0	0	0	0	0	0	1	1 (10)	0	0	1	1 (3,33)	0	0
Transaminase elevation	0	0	0	0	1	1 (10)	0	0	0	0	0	0	1	1 (3,33)	0	0
Hyperkaliemia	1	1 (10)	0	0	0	0	0	0	0	0	0	0	1	1 (3,33)	0	0
Leuco/neutropenia	4	3 (30)	0	0	7	2 (20)	0	0	0	0	0	0	11	5 (16,7)	0	0
Thrombopenia	1	1 (10)	0	0	2	2 (20)	0	0	0	0	0	0	3	3 (10)	0	0

Statistical analyses. Data concerning patients without disease progression or death at last follow-up were censored. Survival curves were estimated using the Kaplan-Meier method, and compared with the log-rank test. The Student's *t*-test was used to compare DCE-MRI related data. All statistical tests were two-sided at the 5% level of significance and analyses were performed using the SPSS 16.0© software for Windows (SPSS Inc™, Chicago, IL, USA).

Results

Patients' characteristics and treatment. Between May 2006 and October 2010, thirty patients were included in the METRO-1 trial. Patients' characteristics are summarized in Table I. Median age was 58.5 years. All patients had advanced cancer of different tumor types (8 breast cancers; 6 urothelial cancers, 5 colorectal cancers, 2 adrenal gland cancers, 2 pancreatic cancers, 2 oesophagus cancers, 2 melanoma, 1 ovarian cancer, 1 cervix cancer and 1 liver cancer) and all cancers were progressive during prior therapy. Seventeen (57%) patients had received radiotherapy as adjuvant for primary tumor or as palliative treatment for metastatic lesions. All but one patients had received systemic chemotherapy with a median number of 2 treatment lines (range=1-7). All patients included in the study received at least 1 dose of chemotherapy. Twenty-eight patients completed at least 1 cycle of chemotherapy (range=0-8).

Dose-limiting toxicity. No DLT was observed during dose escalation. Ten patients were enrolled into each of the three levels of metronomic chemotherapy. Adverse events (AE) reliable to metronomic chemotherapy are shown in Table II. Almost all AEs were limited to grade 1-2 level toxicities. We only observed two grade 3 asthenias for one patient of level 1 and for another patient of level 2.

In the first level of dose, we reported a total of 22 AEs. The two most frequent AEs were neutropenia and fever occurring in 3 patients. All 4 reported leuco/neutropenias were grade 1 AEs with spontaneous recuperation without intervention. Six events of fever were reported with 1 grade 2 and 5 grade 1. None of them necessitated any medical intervention. In the second dose level, 30 events were recorded. Main AEs were linked to haematological toxicity (anemia leuco/neutropenia and/or thrombopenia, 2 patients

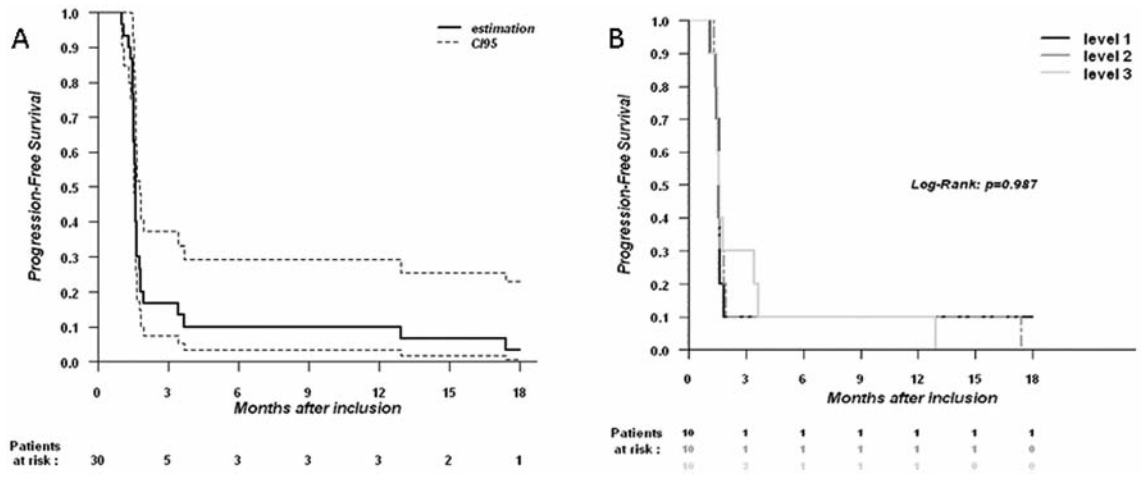

Figure 1. *Progression-free survival for the whole cohort (A) and for each escalation dose level (B).*

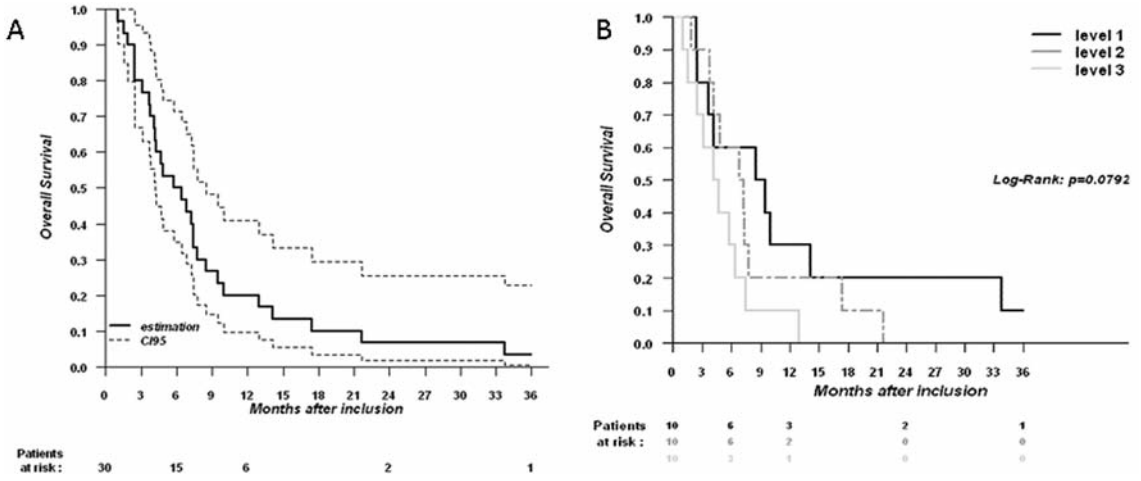

Figure 2. *Overall survival for the whole cohort (A) and for each escalation dose level (B).*

each), digestive toxicity (nausea/vomiting and abdominal pain, 2 patients each). All were grade 1 events except for two grade 2 leuco/neutropenias.

In the third level, there were only 13 AEs, all were grade 1. Among all adverse events described above, some of them are common with interferon therapy-like fever, sweat and reaction at injection site in 3, 3 and 2 patients, respectively. These events were reliable to interferon therapy and thus more unfrequent after escalation of interferon doses.

Treatment continuation and survival. Treatment continuation rate at 4 months was 6.67% (2 out of 30 patients). Best response at 4 months was stable disease for 5 patients (17%). Out of them we observed 1 breast cancer, 2 urothelial tumors, 1 colorectal cancer and 1 adrenal gland cancer. Median PFS was 1.6 months (95% confidence interval=1.5-1.8 months) with no significant difference between the 3 dose escalation levels (Figure 1). It is noteworthy that 3 patients had a prolonged progression-free survival with no event after 12 months of treatment, each in one escalation dose level. Median OS was 6.1 months (95% confidence interval: 4.2-8.5 months). No OS difference could be observed between the three dose levels (Figure 2).

Antiangiogenic effect on DCE-MRI. All 4 MRIs were interpretable for only 3 out of the 30 patients. Imaging was

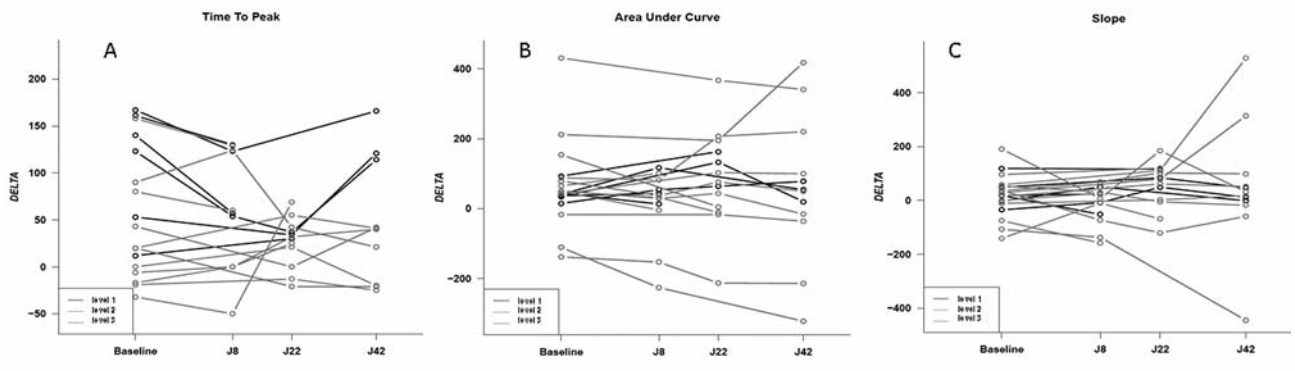

Figure 3. *Individual scatterplots depicting the 3 analyzed DCE-RMI parameters, A: time to peak; B: area under the curve; C: Slope. Delta data were obtained by comparing tumor tissue to adjacent normal tissue.*

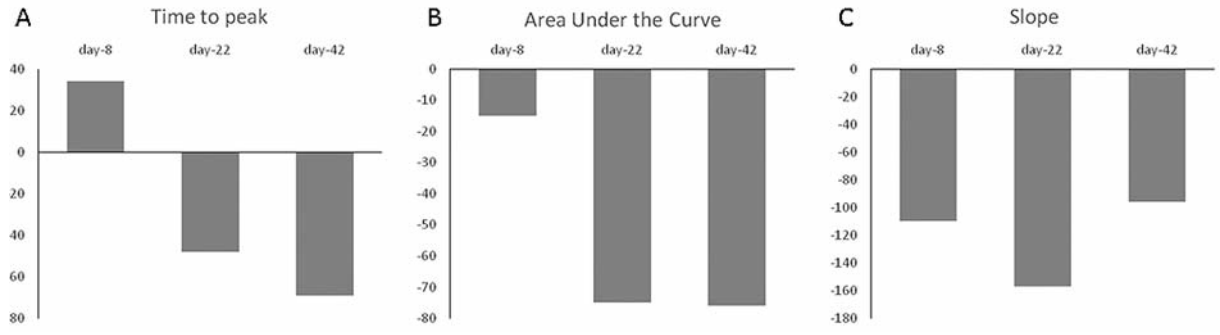

Figure 4. *Graphs representing evolution of the 3 DCE-MRI parameters, A: time to peak; B: area under the curve; C: Slope, compared to their baseline measure for patient ME-01-025.*

interpretable for 20 patients at baseline, 17 patients at day 8, 20 patients at day 22 and 16 patients at day 42. Due to lack of interpretable data and the small sample size at each dose level, statistical analyses were perfomed for the whole cohort. Figure 3 shows individual plots for the three DCE-MRI-related parameters analyzed. For the 11 cases with data available at baseline and day 8, we observed a significant decrease in the "time to peak" after one week of treatment (p=0.036). This decrease could not be confirmed at day 22 and day 42; p-value equal to 0.89 and 0.85 when compared to baseline, respectively. There were no significant differences in the two other analyzed features (area under the curve and slope). Because of the lack of interpretable MRI data, no correlation could be analyzed between DCE-MRI modifications and response to treatment. However, MRI data were interpretable for one of the 5 patients without progression after 12 months, and showed a clear decrease of angiogenesis-related features for this patient at day-8, -22 and -42 (Figure 4).

Discussion

Metronomic chemotherapy was well-tolerated in this phase I prospective study combining low-dose vinorelbine, low-dose cyclophosphamide and interferon-alpha-2b. No serious adverse event could be observed in the 30 patients included in this trial. Toxicities were mainly related to haematological side-effects and well-known interferon-related toxicities (fever, sweat, reaction at injection site). Only two grade 3 AEs corresponding to asthenia were reported. Imputability of treatment to these AEs could be discussed for such patients with heavily-treated advanced refractory malignancies. The present study confirms the safety of this regimen with no toxicity increase following dose escalation.

The major pathway identified in angiogenesis has been VEGF (vascular epithelial growth factor) pathway (5). The main member of this family of growth factor implicated in angiogenesis was VEGF-A. This soluble factor was generally secreted by cancer cells and was able to bind to a

member of a family of transmembrane tyrosine kinase receptors called VEGF receptors. These receptors were present in a high number on the membrane surface of endothelial cells. VEGF-R activation led to activation of intracellular pathways like PI3K-AKT and MAPK pathways in order to stimulate mobilization, migration, proliferation and survival of endothelial cells. Description of this mechanism allowed for development of antiangiogenic agents targeting this pathway. Targeted antiangiogenic therapies like bevacizumab or sunitinib demonstrated their efficacy on clinical parameters like progression-free survival and/or overall survival. These treatments are expansive and toxic and many efforts have been made to identify predictive markers without being able to produce any clear results usable in clinical routine practice (20, 21). Further studies are, thus, warranted to explore the correlation between serum biomarkers evolution and clinical benefit.

By the same time a cheaper way to inhibit angiogenesis has been developed using conventional cytotoxic agents. Conventional chemotherapy was generally administrated using regular treatment courses, where chemotherapy is administered at the maximum tolerated dose, spaced by long rest periods. Rest allowed recuperation of side-effects like myelosuppression, but could also make possible tumor progression through cell proliferation and angiogenesis. The metronomic regimen of chemotherapy is thought to be able to stop this neovascularisation by continuous angiogenesis inhibition. The safety of metronomic chemotherapy has been largely studied in many clinical trials (18, 22). As shown in the present study the main adverse events, correlating to the ones described in the literature, were grade 1-2 nausea, vomiting, asthenia, and haematological AEs. Serious adverse events were rare. These observations allowed the development of metronomic therapy.

Certain published articles tried to identify biological markers correlated to metronomic chemotherapy efficacy. Nevertheless no clear linkage has been yet demonstrated with very discrepant results (23-26).

Another way developed to highlight the antiangiogenic effect of such therapies was functional imaging. The principle relied on the analysis of perfusion parameters before and after injection of contrast agents. The main imaging used in the aera of angiogenic therapy is dynamic contrast-enhancement (DCE)-MRI (27, 28). Targeted therapies like bevacizumab and sunitinib induced significant modification of DCE-MRI parameters upon treatment (29, 30). For metronomic chemotherapy, the antiangiogenic effect of an association of metronomic tegafur/uracil and sorafenib was studied by analyzing DCE-MRI parameters in hepatocarcinoma patients (31). Decrease of the pharmacokinetics parameter K_{trans} (volume transfer constant) in DCE-IRM upon therapy was correlated with tumor response and survival.

We failed to demonstrate an antiangiogenic effect in METRO-1. One possible explanation was the lack of power due to the small number of patient with interpretable DCE-RMI data. Difficulties to analyze DCE-MRI parameters have been largely demonstrated (28). Dynamic parameters suffered from a lack of reproducibility in intra-patient as well as in inter-center assessments. It thus seems that DCE-MRI could not yet be developed in large-scale multi-centre clinical trials. Despite the complexity of DCE-RMI, many efforts have to be made in order to develop this promising biomarker in the area of antiangiogenic therapy.

In conclusion, combination of low-dose vinorelbine, cyclophosphamide and interferon-alpha-2b is a safe regimen. The benefits of antiangiogenic targeted therapies in many cancer types like renal cancer, colon cancer and ovarian cancer were herein presented. The potential antiangiogenic effect of metronomic chemotherapy deserves to be further explored in larger clinical trials in order to confirm efficacy of this well-tolerated and cheap treatment.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

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Received September 15, 2015
Revised October 29, 2015
Accepted October 30, 2015