

**Keywords:** chordoma; gastrointestinal stromal tumour; imatinib; metronomic cyclophosphamide

# A dose-escalating phase I of imatinib mesylate with fixed dose of metronomic cyclophosphamide in targeted solid tumours

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**Background:** Preclinical findings suggest that imatinib mesylate (IM) and metronomic cyclophosphamide (MC) combination provides synergistic antiangiogenic activity on both pericytes and endothelial cells.

**Methods:** We have designed a 3+3 dose-escalating phase I trial with a fixed dose of MC (50 mg two times daily) plus IM (400 mg per day; 300 and 400 mg two times daily). Enrolled patients had IM- and sunitinib-refractory advanced gastrointestinal stromal tumours (GIST) ( $n=17$ ), chordoma ( $n=7$ ) and mucosal melanoma ( $n=2$ ). Dose-limiting toxicities were monitored for the first 6 weeks. Progression-free survival (PFS) and response assessment are based on RECIST 1.0 guidelines. Pharmacokinetics of IM were measured before and after exposure to MC.

**Results:** No dose-limiting toxicity was observed. Fourteen patients of the expanded cohort received 400 mg two times daily of IM with MC. Apart from a case of possibly related acute leukaemia occurring after 4 years of treatment, we did not see unexpected toxicity. No drug–drug pharmacokinetic interaction was observed. There was no objective response. We have observed long-lasting stable disease in chordoma patients (median PFS = 10.2 months; range, 4.2–18+) and short-term stable disease in heavily GIST pretreated patients (median PFS = 2.3 months; range, 2.1–6.6).

**Conclusion:** This combination is feasible and may warrant further exploration in refractory GIST or chordoma patients.

Metronomic chemotherapy refers to the frequent, usually daily, administration of cytotoxic drugs at doses that are significantly less than the maximum-tolerated dose, with no prolonged drug-free breaks. Oral cyclophosphamide-based metronomic chemotherapy is the most largely studied metronomic regimen with more than 30 retrospective studies and phase II trials reporting *in vivo* antiangiogenic and immunomodulatory properties and significant clinical antitumour activity, which has been confirmed in heavily

treated patients that have exhausted all effective treatments (Penel *et al*, 2010, 2012).

Imatinib mesylate (IM) is a potent inhibitor of KIT, 'break-point cluster region'-Abelson' (BCR-ABL), platelet-derived growth factor (PDGFR) and colony-stimulating factor 1 receptor (CSF1R) activities that has marked antitumour activity on chronic myelogenous leukaemia and several other haematological malignancies and solid tumours including gastrointestinal stromal

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tumours (GISTs) (Blay *et al*, 2007), chordoma (Stacchiotti *et al*, 2012), aggressive fibromatosis (Penel *et al*, 2011a) and melanoma harbouring KIT mutation (Guo *et al*, 2011), as well as thymic carcinoma with KIT mutations (Schirovi *et al*, 2012).

Pietras and Hanahan (2005) described the synergistic activity of the combination of metronomic cyclophosphamide (MC) and IM in patient-derived tumour xenograft mouse models. Their study showed that this combination acts as an antiangiogenic treatment, as imatinib interferes with pericyte activity through the inhibition of the PDGFR and oral MC induces the endothelial cell apoptosis. This combination provides an objective response and survival advantage in this mouse model. Until now, the precise antitumour activity of this combination had not precisely determined in humans despite these promising preclinical findings.

In this context, a multi-dose-escalating phase I trial to determine the phase II recommended dose of this combination, to determine the impact of oral MC on the IM pharmacokinetic (PK) and to seek some signs of activity in patients with IM and sunitinib-refractory GIST, with chordoma, life-threatening aggressive fibromatosis or melanoma harbouring KIT mutation was conducted.

## MATERIALS AND METHODS

**Study design.** This is a 3 + 3 dose-escalation study, the primary objective of which is to determine the maximum-tolerated dose of a combination of IM associated with fixed dose of oral MC. The eligibility criteria are listed in Table 1. Tumour response was assessed by RECIST 1.0 every 8 weeks (Therasse *et al*, 2000).

**Dose-escalating process and definition of the maximum-tolerated dose.** Eligible patients received dose-escalated IM (three dose levels: 400 mg daily, 300 mg two times daily, 400 mg two times daily) for 15 days (until steady state) followed by continuous 50 mg day of MC associated with IM. The choice of MC dose was based on widespread evidence of the long-term tolerability of this schedule (Blay *et al*, 2007; Penel *et al*, 2011a). The dose levels of IM have been chosen because of the well-established long-term tolerability of this drug.

Dose-limiting toxicities (DLTs) were assessed during the first 6 weeks of treatment and included an interruption of treatment for more than 4 consecutive days during the first 6 weeks, and the following toxic events (NCI-CTCAE version 3): prolonged (>7 days) grade 4 neutropenia, febrile neutropenia, grade 4 thrombopenia, haemorrhagia related to thrombopenia, grade 3–4 diarrhoea, grade 3–4 rash as well as any kind of unexpected life-threatening toxicities.

We planned an expanded cohort of 14 additional patients at the phase II recommended dose to better explore the tolerability and the activity of this combination (Penel *et al*, 2011b).

**Pharmacokinetic analyses.** Pharmacokinetic analyses were carried out by EC and MM at the Pharmacology-Toxicology Laboratory (University Hospital, Bordeaux, France). Samples had been collected at day 15 (IM alone) and at day 28 (IM + MC). Pharmacokinetic analyses were scheduled before (until steady state) and during the combination at  $T_0$  (predose), 30 min, 1 h, 2 h, 3 h, 4 h, 6 h, 10 h, 11 h, 12 h (day 1) and 24 h. Metronomic cyclophosphamide and IM were quantified in the serum by liquid chromatography-tandem mass spectrometry methods validated according to Federal Drug Agency guidelines. The mass

Table 1. Eligibility criteria

Inclusion criteria	Exclusion criteria
(A) <i>Following cancers:</i> imatinib- and sunitinib-refractory gastrointestinal stromal tumours, chordoma, dermatofibrosarcoma (locally advanced and progressive), metastatic KIT mutation harbouring melanoma, metastatic and progressive cylindroma whatever the primary site, desmoid tumour (life-threatening locations such as progressive mesenteric location or progressive nasocranial location) (B) Metastatic disease or locally advanced disease not amenable to curative intent surgery (C) Disease incurable with standard therapy (D) Measurable disease according to RECIST (1.0) (E) No more than two previous lines of systemic anticancer treatments (4 weeks since the last dose) (F) Four weeks since local therapy (major surgery and last fraction of radiation therapy). Patients must have recovered from toxicity (G) Age $\geq 18$ years (H) PS $\leq$ (ECOG) 2 within the 7 days before the study (I) Albuminaemia $\geq 36 \text{ g l}^{-1}$ and lymphocytes count $> 700 \text{ mm}^{-3}$ (J) Absolute granulocytes $\geq 1500 \text{ mm}^{-3}$ (K) Platelets $\geq 100\,000 \text{ mm}^{-3}$ (L) Total bilirubin within normal limits (M) Serum creatinine within normal limits (N) Normal left ventricular ejection fraction (by MUGA scan or echocardiogram or NT-proBNP dosage) (O) Negative pregnancy test within the 7 days before the study (P) Using effective contraceptive measures (Q) Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial (R) Before patient registration, written informed consent must be given according to ICH/GCP and national regulations	(A) Patients undergoing simultaneous therapy with other anticancer agents (B) Patients with any prior allergy to cyclophosphamide or IM (C) Patients with concurrent illness such a congestive heart failure, active serious infection, etc. (D) Patients not able to stop during the first 2 weeks of treatment (PK phase) any medication that may interfere with PK of either treatments (E) Patients not able to swallow and absorb the oral investigational agents
Abbreviations: ECOG = Eastern Cooperative Oncology Group; ICH/GCP = International Conference on Harmonisation/Good Clinical Practice; IM = imatinib mesylate; MUGA = multigated acquisition; NT-proBNP = N-terminal probrain natriuretic peptide; PK = pharmacokinetic; RECIST = Response Evaluation Criteria In Solid Tumours.	

spectrometer was operated in electrospray ionisation mode with multiple reaction monitoring. Samples (300  $\mu$ l) were prepared by SPE using an MCX Oasis microelution plate (Waters Corporation, Milford, MA, USA), after the addition of an acidic solution (pH 3) containing Internal Standard. The same solid-phase extraction procedure was applied for both methods, but samples were then analysed on different systems: IM was quantified using ultra-performance liquid chromatography coupled with a tandem quadrupole detector (Waters), whereas MC samples were analysed on an Alliance 2695 coupled with Quattro Micro (Waters) (Bouchet *et al*, 2011).

**Ethical considerations.** This study was approved by the regional Ethics Committee ('Comité de Protection des Patients Nord-Ouest II', date of approval: 29 May 2009) and by the French Health Products Safety Agency ('Agence Française de Sécurité Sanitaire et des Produits de Santé', 1 June 2009). This study was registered in the European Clinical Trials Register (EudraCT No. 2008-004212-12). Informed consent was obtained from each patient.

## RESULTS

**Description of the population.** Twenty-six patients were included between February 2009 and January 2011. During the dose-escalation phase, five patients (the first two patients had been replaced because they were not assessable for the PK analysis) have been enrolled at first dose level (IM 400 mg per day), three patients at second dose level (IM 300 mg two times daily) and four patients at the third dose level (IM 800 mg per day). One of the patients enrolled in the third dose level was never treated (died at day 13 days of biguanide overdose). Fourteen additional patients were enrolled in the expanded cohort (IM 800 mg per day). The study population consisted of 20 men (77%) and six women (23%). The median age was 60.5 (range, 41–80) years. The primaries were GIST (17, 65%), sacral chordoma (7, 27%) and mucosal melanoma (2, 8%). The primary locations of GIST were as follows: small intestine (9), stomach (5), rectum (2) and mesenteric (1). Twenty patients (77%) had metastatic disease, mainly involving the liver (16 patients), lung (11 patients) or peritoneum (8 patients). At study entry, the performance status (PS) was as follows: PS = 0 in 11 patients (42%), PS = 1 in 14 patients (54%) and PS = 2 in 1 patient (4%). The previous treatments were surgery in 17 cases (65%), radiotherapy in 5 cases (19%) and previous molecular targeted therapies in 19 cases (73%). One of the two patients with mucosal melanoma had received previous chemotherapy with dacarbazine. Two of the seven patients with chordoma had received previous treatment with IM alone. All patients with GIST have previously been treated with IM alone and sunitinib and had progressed. The other treatments administered to patients with GIST were as follows: sorafenib (11 patients), nilotinib (6 patients), IM + nilotinib (2 patients), masatinib (2 patients) and motesanib (1 patient). All patients experienced progressive disease at study entry.

**Dose escalation.** No DLT was observed during the dose-escalation phase: the third dose level was retained as the recommended dose for further phase II trial: MC 50 mg two times daily plus IM 800 mg per day.

**Tolerance.** One patient enrolled in the expanded cohort was not assessable for safety (died at day 13 of biguanide overdose). The safety profile is detailed in Table 2. Treatment had been suspended for toxicity reason in seven cases (6 out of 14 patients treated at the phase II recommended dose). Doses were reduced for 4 out of 14 patients treated at the phase II recommended dose. One case of acute myeloid leukaemia in a chordoma patient treated with this association for 4 years, thus, a causal relationship is possible.

Table 2. Maximum treatment-related toxicity (n = 25)

Toxicities observed during the trial participation		
Toxicity	Grade 3 No. (%)	Grade 4 No. (%)
Anaemia	3 (12)	0
Neutropenia	1 (4)	2 (8)
Lymphopenia	1 (4)	1 (4)
Thrombopenia	1 (4)	0
Fatigue	3 (12)	0
Anorexia	1 (4)	0
Nausea/vomiting	4 (16)	0
Haematuria	1 (4)	0
Proteinuria	1 (4)	0
Rash/skin toxicity	2 (8)	0
Headache	1 (4)	0
Heart failure	0	1 (4)
Secondary malignancy (acute leukaemia)	0	1 (4)
Toxicity observed during the 42 first days		
Anaemia	1 (4)	0
Fatigue	2 (8)	0
Anorexia	1 (4)	0
Nausea/vomiting	2 (8)	0
Rash/skin toxicity	2 (8)	0
Headache	1 (4)	0
Heart failure	0	1 (4)
National Cancer Institute Common Toxicity Criteria (NCI-CT) version 4 grade 3–4 adverse events in all patients: incidence of maximal toxicity considered by investigator as possibly, probably or definitely related to study drugs. One patient died on day 11 of intercurrent cause (biguanide overdose), and was therefore not assessable for safety.		

**Antitumour activity.** Twenty-five patients were assessable for activity. No objective response was observed during the study. The median progression-free survival (PFS) was 3.4 months (95% CI: 2.5–9) and the median overall survival (OS) was 13.4 months (95% CI: 3.0–16.0 +) in the entire study population. These figures varied widely according to the tumour types. Imatinib mesylate/sunitinib GIST patients experienced a PFS of 2.9 months (95% CI: 2.3–7.6) and an OS of 11.0 months (95% CI: 3.0–16.0). Chordoma patients experienced long-lasting stable disease, whereas all had progressive disease at study entry. The median PFS and median OS were not reached for chordoma patients. The PFS and OS of mucosal melanoma patients were 2.9 and 5.2 months, respectively (see Figures 1 and 2).

**Pharmacokinetic.** The area under the curve for IM correlated to the administered dose (Figure 3). Metronomic cyclophosphamide does not modify the PK parameters of IM (Table 3).

## DISCUSSION

The key findings of this dose-escalating phase I trial were: (i) the phase II recommended dose is MC 50 mg two times daily plus IM 800 mg per day, (ii) this schedule is well tolerated, (iii) MC does not interfere with the IM PK and (iv) tumour growth arrest was

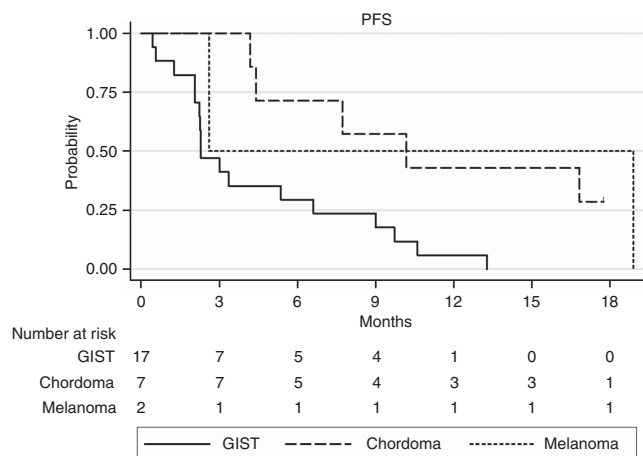


Figure 1. Progression-free survivals by tumour types.

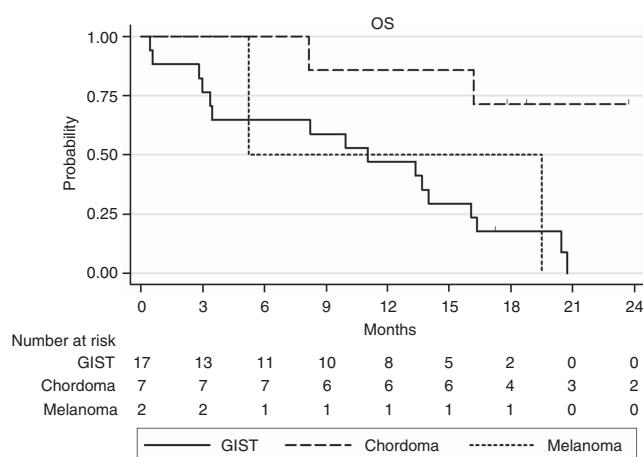


Figure 2. Overall survivals by tumour types.

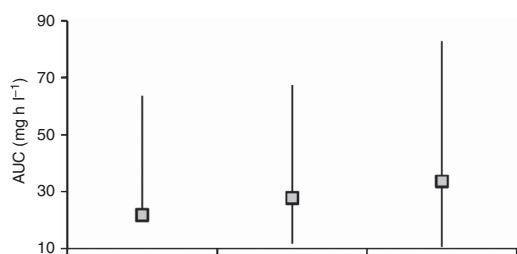


Figure 3. Area under curve (AUC) of imatinib according to the three dose levels: 400 mg daily, 300 mg two times daily, 800 mg daily.

observed in patients with imatinib/sunitib-refractory GIST and chordoma, requiring further clinical investigations.

The tolerance of the combination was mostly manageable without unexpected toxicity. Arterial hypertension and renal toxicity (proteinuria/microscopic haematuria) were only observed in one case. The case of acute leukaemia is possibly related to this combination; cyclophosphamide is a well-established carcinogen (Xu *et al*, 2013). This patient with a massive sacral chordoma was one of the first enrolled patients and received 400 mg per day of IM plus MC after failure of IM alone. This combination provided pain relief and alleviated nerve palsies. After 18 months of treatment, we proposed a drug holiday, but this drug holiday led to severe worsening of pain and nerve palsies. Therefore, this patient received this combination for 5 years (from February 2009 to

PK parameters of imatinib				
PK parameters of imatinib day 15 (monotherapy) vs day 28 (combination)				
	Day 15	Day 28	Differences (%)	P-value
Mean AUC (mg h l <sup>-1</sup> )	33.0	34.3	+ 4.0	0.123
Mean C <sub>max</sub> (ng ml <sup>-1</sup> )	3958.0	4105.0	+ 2.9	0.145
Mean C <sub>0</sub> (ng ml <sup>-1</sup> )	2597.0	2489.0	- 12.3	0.334
Mean T <sub>max</sub> (h)	2.9	2.7	- 10.7	0.302
Mean T <sub>1/2</sub> (h)	14.1	16.4	+ 3.8	0.267

Abbreviations: AUC = area under curve; C<sub>max</sub> = maximum concentration; C<sub>0</sub> = baseline concentration; PK = pharmacokinetic; T<sub>max</sub> = time t to reach maximal concentration; T<sub>1/2</sub> = half-life.

February 2013) without significant toxicity until the diagnosis of acute leukaemia. This patient is currently under treatment for this leukaemia.

We have observed clinically meaningful activity in seven chordoma patients. The median follow-up of the chordoma patients was 23.7 months. The 12-month OS rate was 6/7 and the 12-month progression-free rate was 3/7. The median PFS was not reached. Stachiotti *et al* (2013) have recently reported on a single-arm phase II trial of IM (800 mg per day) in 56 chordoma patients. The objective response rate was 1 of 50 (2%). The median PFS was 9 months (Stachiotti *et al*, 2013). The same team had explored the activity of lapatinib (1500 mg per day) in 18 EGFR-positive chordomas. The median PFS was 8 months, with 6 confirmed partial responses (Stachiotti *et al*, 2013). The IM/MC combination warrants further investigation in chordoma patients.

Seventeen previously heavily treated GIST patients have been enrolled in this trial. In these cases, the PFS was 2.9 months. Growth modulation index (ratio of time to progression (TTP) with the investigational combination divided by the time to progression with the prior treatment) was available in 14 out of 17 GIST patients. The median TTP was 8.2 months (1.2–31.2) with the prior treatment and 2.7 months (0.5–10.5) with the IM/MC combination. Three out of the 14 available patients (21%) experienced a significant growth arrest with a growth modulation index superior to 1.33 (Von Hoff *et al*, 2010). These figures must be compared with the PFS observed in large retrospective study. The rechallenge of IM alone provides a median PFS of 2.9 months. The role of adding MC to rechallenge of IM in heavily pretreated patients have to be studied in an appropriate randomised trial enrolling selected cases (e.g., GIST with multiple mutations or GIST with D842V mutation).

This study demonstrates that adding MC does not interfere with the PK parameters of IM. Up until now, most trials did not document PK interaction in cases of molecularly targeted agent/cytotoxic agent combinations (Giaccone *et al*, 2004; Messersmith *et al*, 2004; Thienelt *et al*, 2005; Sweeney *et al*, 2010; Bousquet *et al*, 2011; De Jonge *et al*, 2011; Awada *et al*, 2013). In a phase I trial, Hamberg *et al* (2010) have found that exposure to ifosfamide (another oxazaphosphorine, such as cyclophosphamide) decreased the exposure to sunitinib. In this trial, the schedule of ifosfamide was conventional (6–9 g m<sup>-2</sup> per 3–4 weeks). In the present trial, the administered dose of cyclophosphamide is very low (50 mg two times daily) in comparison to the doses of cyclophosphamide that have been administered in a metronomic manner.

We have explored the safety of this association, observed some signs of activity and measured the impact of adding MC on

IM PKs parameters. This combination warrants further clinical exploration in chordoma patients and, to a lesser extent, in heavily pretreated GIST patients.

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