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LETTER TO THE EDITOR

Pharmacokinetic profile of imatinib mesylate and *N*-desmethyl-imatinib (CGP 74588) in children with newly diagnosed Ph+ acute leukemias

Elena Marangon · Marco Citterio · Federica Sala · Elena Barisone · Alma Augusta Lippi · Carmelo Rizzari · Andrea Biondi · Maurizio D'Incalci · Massimo Zucchetti

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Dear Editor,

Because of the rarity of childhood Philadelphia chromosome-positive (Ph+) leukemias, data on imatinib pharmacokinetics in children are scant. Imatinib pharmacokinetics were reported in a limited number of leukemic children receiving drug in doses of 260–570 mg/m^2 per day [1].

Despite a wide inter-patient variability, the plasma drug levels were similar to those reported in adult patients treated with standard doses of 400–600 mg/day [2–5]. No data were provided on the pharmacokinetics of the main circulating metabolite of imatinib, *N*-desmethyl-imatinib (CGP 74588), that had already been determined in adults [2, 6].

Ph+ childhood leukemia is less sensitive to imatinib than adult CML and this is likely to be due to major biological differences between these leukemias. However, the different sensitivity may at least partly be related to different bioavailability, metabolism and pharmacokinetic features of imatinib in children and adults that might require adjustment of doses and schedules.

In our study, we determined the pharmacokinetics of imatinib and CGP 74588 in three children (two females and one male, aged 11, 15 and 6 years, respectively), with newly diagnosed Ph+ ALL treated according to the induction phase of the EsPhALL (European intergroup study on post-induction treatment of Ph+ ALL) protocol and in one female child (aged 6 years) with CML in lymphoblastic phase. Imatinib was administered at the dosage of 300 mg/m^2 per day in all patients. They were treated in different Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) centers: Monza, Turin and Florence. The Institutionals Ethical Board approved the study, conducted in accordance with the Helsinky declaration of Principle.

Patient four merits more detail: male, 6 years old, Ph+ ALL. Three days after starting the induction phase Ib according to the EsPhALL protocol (cyclophosphamide, cytarabine, imatinib 300 mg/m^2 per day × 28 days administered orally, dissolved in apple juice), the patient developed a neurologic disorder, with asthenia, drowsiness, slowed speech and aphasia, with negative neuroimaging. Chemotherapy and imatinib were suspended, until full spontaneous clinical recovery; 25 days later, imatinib was restarted, initially at half of full dose (a new pharmacokinetic study was carried out when therapy restarted), then 70% and, finally, at full dose. This time the drug was taken orally, by swallowing the whole capsule. The patient underwent stem cell transplant and died due to treatment-related toxicity.

For the pharmacokinetic study, blood samples were collected at pretreatment (before the morning dose) and 0.5, 1, 2, 4, 8 and 24 h after the first dose and after at least one week of daily doses, presumably when the plasma imatinib concentration achieved steady-state.

E. Marangon (✉) · F. Sala · M. D'Incalci · M. Zucchetti
Laboratory of Cancer Pharmacology,
Department of Oncology,
Istituto di Ricerche Farmacologiche "Mario Negri",
Milan, Italy
e-mail: marangon@marionegri.it

M. Citterio · C. Rizzari · A. Biondi
Department of Pediatric Hematology-Oncology,
University of Milano Bicocca, S. Gerardo Hospital,
Monza, Italy

E. Barisone
Department of Pediatric Hematology-Oncology,
Regina Margherita Hospital, Turin, Italy

A. A. Lippi
DPT Hematology-Oncology,
AOU Meyer-University of Florence, Florence, Italy

Plasma concentrations of imatinib and its major metabolite, CGP 74588, were determined by HPLC-MS/MS [7]. After addition of [D_8]-imatinib as internal standard, the analytes were extracted from plasma using protein precipitation with acetonitrile. The mass spectrometer (Micromass Quattro Ultima Pt triple quadrupole) operated in positive and in selected reaction-monitoring mode and, after HPLC separation, the peak areas corresponding to the *m/z* 494 → 394 transition for imatinib and *m/z* 480 → 394 for CGP 74588 were measured relative to the *m/z* 502 → 394 reaction of the internal standard. The limit of quantitation was 30 ng/mL for both analytes and recoveries were >85%. Pharmacokinetic parameters were calculated using WinNonlin Pro Node 4.1 software (Pharsight Co, Mountain View, CA, USA). Alpha-1-acid glycoprotein (AAG) was measured in plasma using the TT4 Turbitimer Dade–Behring for the quantitative determination of plasma proteins [8].

Plasma concentrations of imatinib and CGP 74588 in children on day 1 and at steady state after daily doses of 300 mg/m^2 are reported in Fig. 1. The pharmacokinetic parameters of the drug and metabolite, derived from the plasma concentration versus time, are summarized in Table 1. Three children received the drug in the form of capsules and for the fourth child it was dissolved in apple juice. On day 1, imatinib achieved a C_{max} (mean ± SD) of 6.19 ± 2.47 μg/mL (range 4.42–9.72 μg/mL) around 4 h after treatment, and 24-h area under the concentration versus time curve ($AUC_{24\,h}$) of 85.11 ± 26.62 μg/mL per h (range 61.71–122.47 μg/mL per h). These values show a wide range and were higher than those reported by Champagne et al. at similar doses of 260 and 340 mg/m^2 (C_{max} 3.6 ± 2.0 and 2.5 ± 0.9 μg/mL; $AUC_{24\,h}$ 51.0 ± 34.9 and 32.1 ± 13.0 μg/mL per h). The highest levels of imatinib were in patient 4, with C_{max} 9.72 μg/mL and $AUC_{24\,h}$

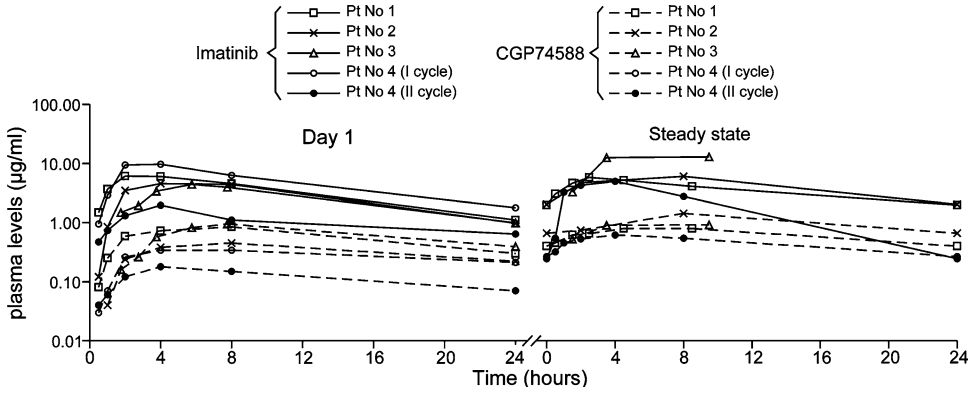

Fig. 1 Plasma concentration–time curves of imatinib and CGP 74588 on day 1 and at steady state in children receiving 300 mg m^{-2} day^{-1} of the drug

Table 1 Pharmacokinetic parameters of imatinib and CGP 74588 on day 1 and at steady state

Imatinib	Day 1				Steady state			
Patient (No)	C_{max} (μg/mL)	$AUC_{0-24\,h}$ (μg/mL per h)	$T_{1/2}$ (h)	AAG (mg/mL)	C_{ss} (μg/mL)	AUC_{ss} (μg/mL per h)	$T_{1/2}$ (h)	AAG (mg/mL)
1	6.05	84.70	8.1	0.44	5.10	77.54	14.4	0.97
2	4.56	71.57	8.4	1.41	5.35	92.08	10.4	1.29
3	4.42	61.71	8.3	0.84	11.30	83.08[a]	–	1.60
$4_{cycle\ I}$	9.72	122.47	8.4	2.17	–	–	–	–
$4_{cycle\ II}$	1.97	24.90	14.0	0.83	4.42	48.18	4.7	0.86
CGP 74588	Day 1				Steady state			
Patient (No)	C_{max} (μg/mL)	$AUC_{0-24\,h}$ (μg/mL per h)	$T_{1/2}$ (h)	MR[b] (%)	C_{ss} (μg/mL)	AUC_{ss} (μg/mL per h)	$T_{1/2}$ (h)	MR[b] (%)
1	0.84	14.07	11.0	17	0.73	14.09	15.8	18
2	0.46	7.87	15.5	11	1.30	22.44	14.7	24
3	0.94	14.72	12.7	24	0.84	6.67[a]	–	8
$4_{cycle\ I}$	0.34	6.63	27.4	5	–	–	–	–
$4_{cycle\ II}$	0.18	2.88	15.0	12	0.57	9.93	16.5	21

[a] $AUC_{0-8\,h}$

[b] Metabolic ratio: $AUC_{CGP\ 74588}/AUC_{imatinib} \times 100$

122.47 μg/mL per h. After repeated doses, at steady state, patients 1 and 2 had C_{max} and $AUC_{24\,h}$ similar to day 1 and patient 3 had C_{max} and AUC about 2.5 times higher than on day 1.

Previous reports in adults with leukemia or gastrointestinal stromal tumor indicate that AAG plasma levels influence imatinib pharmacokinetics [8, 9] and for this reason, we determined the concentration of this protein on the day when pharmacokinetics were studied (Table 1). In view of the small number of cases we cannot establish a relationship between AAG concentration and drug plasma levels, but in two cases, patient 4 (cycle I) and patient 3 (steady state), who had the highest concentration of protein, we also found the highest C_{max} and AUC. Patient 4 with the highest C_{max} and the highest AUC, had a high-protein concentration too (2.17 mg/mL), more than twice normal (0.4–1.0 mg/mL). This child had to suspend therapy because of neurological disorders. After 1 month, the patient showed improved clinical conditions with a normal level of AAG (0.83 mg/mL) and treatment was restarted, giving a half-dose of the drug (150 mg/m^2). In this situation, we repeated the pharmacokinetic study, finding C_{max} 1.97 μg/mL on day 1, C_{ss} 4.42 μg/mL on day 14, and $AUC_{24\,h}$ 24.90 μg/mL per h on day 1 and 48.18 μg/mL per h at steady state, perfectly in line with the other children who had normal AAG values, considering that the dose was only half. Among the patients with repeated treatment, the highest C_{ss} (11.30 μg/mL) and AUC_{ss} (available up to 8 h: 83.08 μg/mL per h) were in patient 3, whose AAG value was 1.6 mg/mL.

The present study shows, for the first time, the pharmacokinetics of the main plasma metabolite of imatinib, CGP 74588 in children. Although the pharmacological activity of this metabolite is the same as that of the parent drug and the metabolic clearance of imatinib in adults accounts for 5–20% of total body clearance [2, 3, 6], it was nevertheless important to investigate the metabolism of imatinib in children, also considering potential drug interactions. The drug is metabolized in liver mainly by CYP3A4 and CYP3A5 enzymes and may interfere with the metabolism of other drugs (during poly-chemotherapy, for example, with cyclophosphamide) or herbal products which inhibit or induce these enzymes [2, 10–12]. The consequence of these interactions due to CYPs inhibition or induction has to be considered in the drug's pharmacological effect.

On day 1 CGP 74588 was detectable in plasma at 30 min, achieving C_{max} 0.64 ± 0.29 μg/mL (range 0.34–0.94 μg/mL) and $AUC_{24\,h}$ 10.82 ± 4.16 μg/mL per h (6.63–14.72 μg/mL per h). The ratio of the plasma concentrations of the metabolite to the parent drug, expressed as a percentage of the metabolic ratio ($MR = AUC_{CGP\ 74588}/AUC_{imatinib} \times 100$) on day 1 ranged from 5 to 24% and was similar (8–24%) at steady state. These ranges were comparable to the range in adults, 5–20% [2–6]. Looking at the elimination of the metabolite, its half-life ranged between 11.0 and 27.4 h on day 1 and was about 16 h at steady state, similar to the values for the parent drug. These data differ from what is reported in adults where the metabolite showed a longer elimination kinetics than the parent drug [2, 3, 6].

Considering that CGP 74588 is as potent as its parent drug in inhibiting Abl-Bcr kinase and that its AUC is 5–24% of the parent drug's AUC, the role of the metabolite in the antileukemic activity of imatinib is probably low in children, as previously reported in adults, and the faster elimination in children probably has no major implications for the pharmacological activity of imatinib.

The relevance of AAG levels for imatinib clearance in children remains an open question calling for further studies.

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