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CLINICAL TRIAL REPORT

Clinical usefulness of therapeutic concentration monitoring for imatinib dosage individualization: results from a randomized controlled trial

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Abstract
Purpose This study assessed whether a cycle of "routine" therapeutic drug monitoring (TDM) for imatinib dosage individualization, targeting an imatinib trough plasma concentration (C_{min}) of 1,000 ng/ml (tolerance: 750–1,500 ng/ml), could improve clinical outcomes in chronic myelogenous leukemia (CML) patients, compared with TDM use only in case of problems ("rescue" TDM).
Methods Imatinib concentration monitoring evaluation was a multicenter randomized controlled trial including adult patients in chronic or accelerated phase CML receiving imatinib since less than 5 years. Patients were allocated 1:1 to "routine TDM" or "rescue TDM." The primary endpoint was a combined outcome (failure- and toxicity-free survival with continuation on imatinib) over 1-year follow-up, analyzed in intention-to-treat (ISRCTN31181395).
Results Among 56 patients (55 evaluable), 14/27 (52 %) receiving "routine TDM" remained event-free versus 16/28 (57 %) "rescue TDM" controls ($P = 0.69$). In the "routine TDM" arm, dosage recommendations were correctly adopted in 14 patients (median C_{min}: 895 ng/ml), who had fewer unfavorable events (28 %) than the 13 not receiving the advised dosage (77 %; $P = 0.03$; median C_{min}: 648 ng/ml).
Conclusions This first target concentration intervention trial could not formally demonstrate a benefit of "routine TDM" because of small patient number and surprisingly limited prescriber's adherence to dosage recommendations.

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Favorable outcomes were, however, found in patients *actually elected* for target dosing. This study thus shows first prospective indication for TDM being a useful tool to guide drug dosage and shift decisions. The study design and analysis provide an interesting paradigm for future randomized TDM trials on targeted anticancer agents.

Keywords Individualized medicine · Protein kinase inhibitors · Drug monitoring · Pharmacokinetics · Medication adherence

Introduction

The tyrosine kinase inhibitor (TKI) imatinib (Gleevec®, Glivec®; Novartis Pharma, Basel, Switzerland) is a first-line treatment of chronic myeloid leukemia (CML) and has impressively improved the survival of CML patient [1, 2]. Second generation TKIs become increasingly available, showing a reduction in disease progression rates, yet without clear survival advantage [3]. Imatinib is prescribed at fixed dosage of 400 mg once daily in chronic phase CML and 600 mg in accelerated phase, but discussions about the optimal dose are still ongoing [4–6]. In practice, more than 30 % of patients discontinue imatinib because of unsatisfactory efficacy or intolerance [7, 8], which might be partly overcome by appropriate dosage modifications [9].

The systematic use of high-dose imatinib as standard treatment has not demonstrated a risk-benefit improvement, as it increases toxic effects without clear therapeutic advantage [10]. Individualized dosage approaches are not well defined [11]. The prescribing information [12] and treatment recommendations [13, 14] mention dosage individualization based on the follow-up of adverse events (AEs) and response markers. Those *pharmacodynamic* markers, namely hematologic, cytogenetic and molecular responses, are surrogate predictors of overall survival, event-free and progression-free survival [14].

Several authors have suggested as well to use circulating imatinib concentrations as a *pharmacokinetic* predictor of response, to be monitored for dosage individualization (therapeutic drug monitoring, TDM) [15–17]. Inter-patient variability of imatinib pharmacokinetics is indeed important, with trough concentrations (C_{min}) varying by 55–106 % between patients under a given dosage [18]. The standard dosage is thus expected to produce sub- or supratherapeutic drug exposure in a significant fraction of patients [9, 14, 18]. Since imatinib C_{min} correlates with pharmacodynamic response [18–20], TDM has been proposed for selected cases with clinical concerns (called "rescue TDM" thereafter), e.g., to evaluate drug–drug interactions, acute adherence problems [14] or potential sources of suboptimal efficacy or tolerance [15, 17, 21]. Despite the limited evidence supporting the usefulness of this "rescue TDM" to *correct* such issues, efforts have been made during the past years to offer it to problematic patients. An ounce of prevention being worth a pound of cure, one might consider offering TDM-based dosage adjustment to all patients receiving imatinib. However, to date, a formal evaluation of "routine TDM" of imatinib is lacking [22] regarding its usefulness to *prevent* unfavorable outcomes. In addition, prospective randomized controlled trials validating the proposed therapeutic concentration ranges are still awaited [23, 24].

Therefore, we set up a prospective randomized trial aiming to evaluate whether a "routine TDM" intervention with dosage adjustment, targeting imatinib C_{min} of 1,000 ng/ml [17, 18] (tolerance interval: 750–1,500 ng/ml) could keep patients away from treatment failure, moderate to severe AEs or treatment discontinuation. Given that "rescue TDM" was already available in case of unsatisfactory therapeutic response, ethical considerations made us decide not to deny TDM access to patients in the control group, but to merely limit "rescue TDM" to an on-need basis.

Methods

Study design and patients

Imatinib concentration monitoring evaluation (I-COME) was an investigator-initiated, multicenter, parallel, open-label, randomized Swiss study [19]. It included CML patients aged ≥18 years, in chronic or accelerated phase, receiving imatinib since ≤5 years. Patients were recruited by hospital and ambulatory care hematologists. The protocol was approved by appropriate regional Swiss ethics committees [25].

Randomization and masking

Patients were randomly assigned (1:1) to either the intervention ("routine TDM") or the control group ("rescue TDM") by the coordinating center (Division of Clinical Pharmacology, Lausanne). Scratch-off concealed allocation lists were used, based on variable size block randomization stratified in three layers, corresponding to the duration of

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imatinib treatment (0–18/>18–36/>36–60 months). Neither the investigators nor the patients were blinded for treatment assignment.

Procedures

A plasma sample was drawn for study inclusion during a regular medical visit from all patients having given their informed consent. The sample was advised to be drawn ≥4 h after drug intake and was sent to the coordinating center for imatinib concentration measurement, where patients were randomized, along with a laboratory request which simultaneously served as case report form for drug administration details, treatment response and tolerance. A validated Bayesian method was used to extrapolate the measured concentration to C_{min} [26]. All patients were asked a last blood sample after 1 year.

Patients allocated to the *control group* received neither the result of their imatinib concentration nor a dosage recommendation at study inclusion, unless specifically requested because of clinical concerns ("rescue TDM").

For patients allocated to the *intervention group* ("routine TDM"), a dosage recommendation was given to practitioners targeting a C_{min} of 1,000 ng/ml [19, 20] (tolerance interval 750–1,500 ng/ml). Additional TDM could be requested at any time, and a control measurement was recommended in case of dosage change or suspected non-compliance, after at least 1 week of regular drug intake to ensure steady-state attainment. In the absence of established upper concentration limits, dosage decrease was only proposed if C_{min} > 1,500 ng/ml went along with moderate (grade 2) clinical or severe (grade 3) laboratory AEs (according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0). The procedure of dosage recommendations is summarized and illustrated in Fig. 1.

Imatinib plasma concentrations were measured by liquid chromatography–tandem mass spectrometry (LC–MS/MS) [27, 28]. AEs were graded by the physician in charge and reported along with TDM requests. Assessments of cytogenetic and molecular response were performed as usual and collected by the investigators. Due to varying analytical sensitivities, BCR-ABL/ABL results were censored at <0.01 % IS (10^{-4}). Complete cytogenetic response (CCR) was assumed under BCR-ABL/ABL values <1 % IS [29] when no measurement was available.

Statistical analysis

Analyses were performed according to intention-to-treat. The *primary endpoint* was the percentage of patients remaining event-free during the 1-year study follow-up, i.e., remaining without treatment failure [4], disease progression, occurrence of moderate clinical or severe laboratory AEs, or treatment discontinuation. A sample size of 300 patients was targeted (90 % power at the 5 % significance level for a decrease from 35 to 20 %, two-sided χ^2 test). The study had, however, to be closed after the scheduled recruitment period of 2 years with only 56 patients included. The primary outcome was also described as time-to-event variable using Kaplan–Meier plots. Given that half of the patients in the intervention group did not or only partially receive the recommended dosage (Fig. 2), a post hoc exploratory subgroup analysis of the primary outcome was performed in this group.

Secondary endpoints were as follows: percentage of patients achieving major molecular response (MMR) and CCR, remaining without moderate AEs, presenting clinical concerns at inclusion and improving over 1 year, with imatinib C_{min} above 1,000 ng/ml [19, 20]/within tolerance interval (Fisher's exact test); median reduction of BCR-ABL/ABL transcripts (Friedman test); predictive performance of total and free C_{min} for failure and AEs as defined in the primary endpoint (details are provided in the *Online Resource 1*); and compliance of practitioners toward dosage advice. Planned correlations of co-medication and genetic factors influencing imatinib pharmacokinetics with clinical outcomes could not be analyzed due to limited patient number.

The study was registered with Current Controlled Trials, number ISRCTN31181395.

Role of the funding source

A research grant and logistic support for the study was provided by Novartis (Bern, Switzerland). The study was also partly financed by the Swiss National Science Foundation (Nano-Tera initiative, ISyPeM project). The trial sponsor (Division of Clinical Pharmacology, Lausanne) had full responsibility for the study design, data collection, analysis, interpretation and manuscript writing. The data are the property of the sponsor, but Novartis was granted access to anonymized study data. Novartis had no role in the design and analysis of the trial, result interpretation and final content. None of the authors were paid for manuscript writing. The authors had full access to all the study data and had the final responsibility and decision to submit the manuscript for publication.

Results

Study population

Between September 1, 2009 and August 30, 2011, 56 patients were included and randomized (Table 1). Median duration of imatinib treatment at inclusion was 21 months,

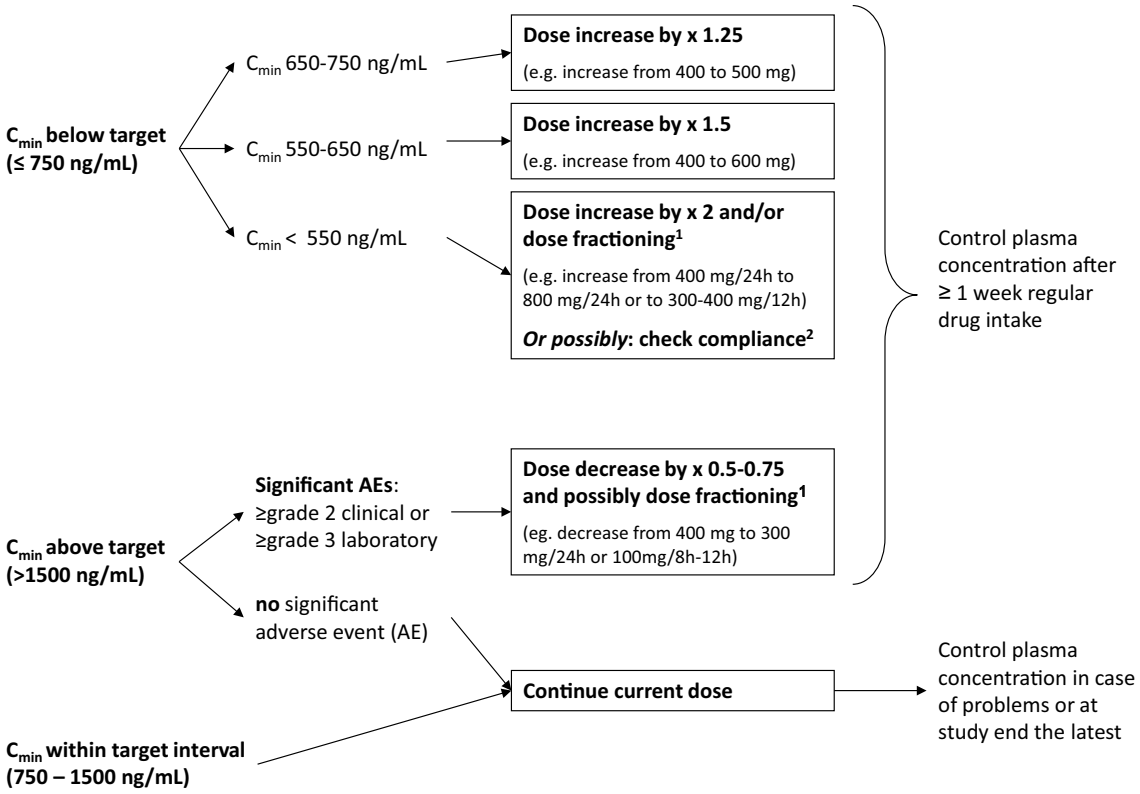

Fig. 1 Schematic representation of dosage recommendation procedure. [1]Fractioning the total daily dose into two intakes allows achieving higher C_{min} and lower C_{max} than under a single intake per day. [2]A compliance check was especially proposed if the concentration was unexpectedly low considering age, body weight and gender [18, 34]

and median duration of study follow-up 13 months. In the "routine TDM" group, 15/28 of patients received the recommended dosage, 6/28 did not and 7/28 only partially (Fig. 2). In the control group, 12/28 patients requested "rescue TDM" during the study, including 8 already at inclusion (Fig. 2). In total, 13 patients (23 %) discontinued imatinib during the study period because of efficacy concerns ($N = 8$) or tolerance problems ($N = 5$), which were already present at inclusion in three and four patients, respectively (details: Table 4).

Mean daily imatinib dose at study inclusion was 404 mg, with 45/56 (80 %) of patients receiving 400 mg, and six and five patients receiving lower and higher doses, respectively. During the study, dosage increase and decrease was proposed to 24 and 4 patients, respectively (17 and 2 to "routine," 7 and 2 to "rescue" TDM patients, respectively; mean daily dosage recommended: 485 mg). At study end 7/43 (63 %) of patients remained on standard dose imatinib, while 3 and 13 patients received lower and higher doses, respectively (mean daily dosage: 444 mg).

Measured plasma concentrations and individual predicted C_{min} are illustrated in the *Online Resource 2*, and AEs reported during the study are listed in Table 2.

Primary outcome

Globally, 13/27 of patients receiving "routine TDM" remained event-free during the study course (48 %), compared with 16/28 patients receiving only "rescue TDM" (57 %; absolute risk difference: +9 %, 95 % confidence interval: [−21 to +39 %], $P = 0.69$). Out of those, 6/27 patients (21 %) in the "routine TDM" and 5/28 (18 %) in the "rescue TDM" group are presented already with an event at inclusion. In the subgroup analysis of the "routine TDM" group, 10/14 of patients receiving the recommended dosage after one cycle of TDM remained event-free (71 %), compared with 3/13 patients who did not or only partially receive the recommended dosage (23 %; absolute risk reduction: −48 % [−8 to −89 %], $P = 0.033$). A longitudinal presentation is shown in Fig. 3.

Secondary outcomes

The decline of median BCR-ABL/ABL transcript levels was rather small in both groups (0.48 $\log_{10}$ reduction in the control, 0.32 $\log_{10}$ reduction in the intervention group, $P = 0.32$). There were no differences

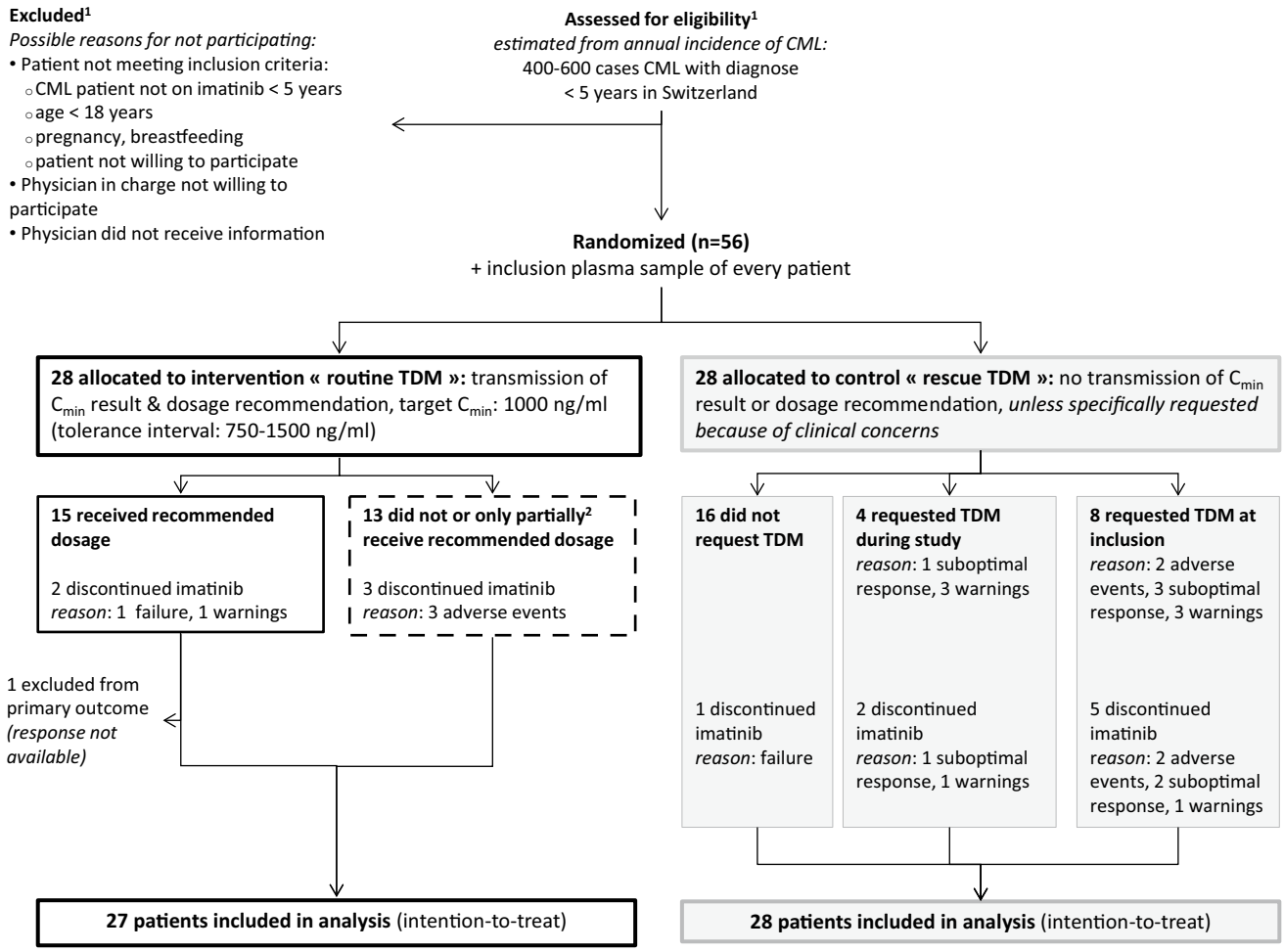

Fig. 2 Trial diagram. TDM, therapeutic drug monitoring. *Solid black boxes* intervention group ("routine TDM" at inclusion). *Gray boxes* control group ("rescue TDM" only). *Dashed black box* routine TDM patients having not or only partially received the recommended dosage during the study. [1]No absolute numbers can be given due to the multicenter study design having proposed the study to both clinic- and practice-based hematologists throughout Switzerland. [2]Patients having only *partially* received recommended dosage ($n = 8$) include patients that either received a dosage change following our recommendation, but *not the exact* recommended dosage, or received the recommended dosage *with a sizeable delay*. Patients *not* having received recommended dosage did never receive any dosage according to our recommendations

between groups with respect to other secondary clinical outcomes or in C_{min} at study end (Table 3). In the "routine TDM" group, 9/13 (69 %) of patients who received recommended dosage had C_{min} in the target range at study end versus 4/10 (40 %) of those who did not or only partially receive the recommended dosage (Fig. 4). Cumulative efficacy and toxicity events did not differ statistically between patients with average high or low (≥/<median) total or unbound imatinib C_{min}. However, there was a trend toward a higher proportion of treatment failures in patients with lower unbound C_{min}. Conversely, AEs tended to be more frequent in patients with higher unbound C_{min} (Online Resource 2). Secondary outcomes and dosage modifications during the study are illustrated in Online Resource 2.

Discussion

I-COME is the first randomized controlled trial having prospectively investigated the clinical benefit of one cycle of "routine TDM" for dosage individualization of imatinib targeting a C_{min} of 1,000 ng/ml [19, 20] (tolerance interval: 750–1,500 ng/ml). Such a trial has been repeatedly called for in CML patients receiving imatinib and for other targeted anticancer agents [21–24, 30]. The trial was not able to demonstrate a significant benefit of "routine TDM" in comparison with usual treatment management ("rescue TDM" only in case of clinical problems), in terms of event-free survival (combined efficacy, safety and persistence outcome) after 1-year follow-up. The main study limitations are the low number of patients enrolled and the limited prescriber's

Table 1 Patient and sample characteristics

	Control group ($N = 28$)	Intervention group ($N = 28$)
Patient characteristics		
Male:female (*N*)	15:13	13:15
Age (years)	53 (44–64)	59 (49–73)
Body weight (kg)	72 (64–87)	77 (63–84)
Duration of imatinib treatment at inclusion (months)		
0–18 months (*N*)	11	12
>18–36 months (*N*)	10	10
>36–60 months (*N*)	7	6
Months since initial CML diagnosis at inclusion	19.5 (7.8–35.5)[a]	24.5 (6.8–34)[a]
Sokal score (*N*)		
High (>1.2)	1	7
Medium (0.8–1.2)	14	10
Low (<0.8)	7	7
Not available	6	4
Initial treatment other than standard dose imatinib (*N*)		
Imatinib >400 mg	1	1
Hydroxyurea pretreatment	7	9
Interferon	1	2
Imatinib daily dose at inclusion		
<400 mg	0	6
400 mg	24	20
>400 mg	4	2
Sample (imatinib concentration) characteristics		
Total numbers of samples[b] (*N*)	60	81
Patients with at least 1 sample (inclusion sample)	28	28
Patients with at least 2 samples	25	25
Patients with 3 samples or more	5	17
Imatinib daily dose		
<400 mg	0	17
400 mg	45	46
>400 mg	15	18
Measured total imatinib concentration (ng/ml)	1,612 (1,118–2,139)	1,093 (747–1,555)
Measured unbound imatinib concentration (ng/ml)	46 (32–67)	30 (21–47)
Time after last dose intake (h)	7.8 (4.5–16.1)	13 (6.5–22.2)
Predicted imatinib total C_{min} (ng/ml)[c]	801 (610–1,107)	758 (578–1,013)
Predicted unbound imatinib C_{min} (ng/ml)[d]	22 (13–31)	23 (18–30)
α1-acid glycoprotein concentration (g/l)	0.89 (0.75–1.04)	0.84 (0.76–1.00)

Continuous variables are summarized as median (interquartile range)

C_{min}, imatinib trough concentration; n, number of patients

[a] Not significantly different (22.9 vs. 23.1 months, $P = 0.96$, Welch *t* test)

[b] The number of samples corresponds to the number of TDM occasions in the respective group, which is higher in the intervention group through the study design (in the intervention group TDM could be performed at any time and results were always transmitted; in the control group samples were requested at inclusion and study end only; TDM results during the study were only transmitted on specific request in case of clinical concerns)

[c] Predicted using a validated Bayesian TDM method, taking into account gender, body weight and age for prior predictions Gotta et al. [26]

[d] Predicted using a population PK model taking into account α1-acid glycoprotein concentrations (Haouala et al. 2012)

adherence to dosage recommendations in the "routine TDM" group. Only 50 % of patients allocated to routine TDM intervention actually received the recommended imatinib dosage, which was nevertheless associated with better achievement of target concentrations and reduced risk (−48 %) of unfavorable events (treatment failure, moderate clinical or severe laboratory AEs or imatinib discontinuation).

Limited feasibility of adequate patient recruitment in such trials has been previously reported [31]. This may be mainly attributable to the outpatient setting and the response and tolerability being considered satisfying in most patients. Additionally, the emergence of second generation TKIs may have reduced the interest for imatinib dosage optimization interventions. Such interventions remain rather complex and time-consuming—according to either pharmacodynamic or pharmacokinetic response markers. In our study, the relatively longtime elapsing between routine medical visits (usually 3 months) might have complicated dosage adjustments, despite oral and written communication of recommendations. Moreover, TDM hardly belongs at present to the culture of oncological patient management.

Table 2 Adverse events reported during the study in the 56 patients included

	Total ($N = 56$)		TDM group ($N = 28$)		Control group ($N = 28$)		P value
	Any grade n (%)	Grade 2 (grade 3)	Any grade (n)	Grade 2[3] (n)	Any grade (n)	Grade 2[3] (n)	Fisher's exact test
Hematologic/laboratory adverse events[a]							
Anemia	24 (43 %)	1 (2 %)	14	–	10	1	0.60
Neutropenia	7 (13 %)	1 (2 %) [1 (2 %)]	4	−[1]	3	1	1
Thrombocytopenia	7 (13 %)	1 (2 %)	5	1	2	–	0.43
Increased liver enzymes	7 (13 %)	1 (2 %)	5	–	2	1	0.43
Clinical adverse events[a]							
Fluid retention/peripheral edema	28 (50 %)	5 (9 %)	14	4	14	1	1
Muscle cramps/arthralgia	24 (43 %)	6 (11 %)	16	3	8	3	0.30
Fatigue/weakness/insomnia	19 (34 %)	6 (11 %)	10	2	9	3	1
Diarrhea/abdominal cramps	13 (23 %)	2 (4 %)	8	2	5	–	0.54
Skin rash/pruritus	10 (18 %)	3 (5 %)	8	2	2	1	0.097
Nausea/vomiting/dyspepsia	8 (14 %)	2 (4 %)	5	2	3	–	0.71
Headache/dizziness	3 (5·4 %)	0	1	–	2	–	1

N total number of patients

[a] The maximum grade for each patient is reported. n: number of patients with adverse event

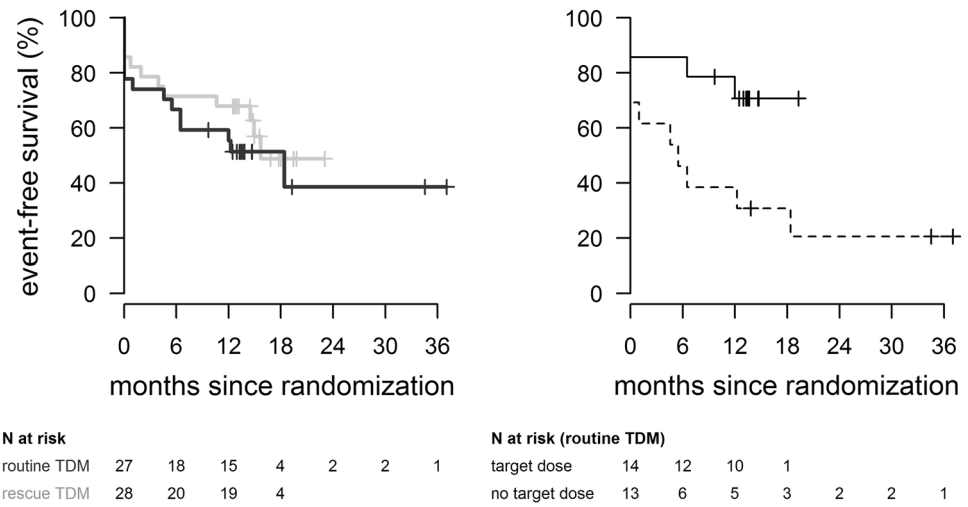

Fig. 3 Longitudinal presentation of the primary outcome (Kaplan–Meier plots): patients remaining event-free, i.e., without failure, occurrence of moderate (grade 2) clinical or severe (grade 3) laboratory adverse events, or discontinuation of treatment. **a** Intention-to-treat analysis: number of events in the control group 12/28 (*gray line*) versus 14/27 in the intervention group (*black line*). **b** Subgroup analysis in intervention group: number of events in patients who received recommended dosage 4/14 (*solid black line* = per-protocol) versus patients who not or partially received recommended dosage 10/13 (*dashed black line*)

The event rate according to the primary outcome was higher than expected in this treatment experienced patient population receiving imatinib since a median of 1.5–2 years. Importantly, about half of the events represented imatinib discontinuation, with 23 % of patients in total having stopped the drug during the 1-year follow-up (compared with 28 % during 5 years reported [32]), probably encouraged by the availability of second generation TKIs [33]. We acknowledge that this could additionally be attributed to one of the following reasons: First, the trial

Table 3 Secondary outcomes

	Control group ($N = 28$) [% (*n*/*N*)]	Intervention group ($N = 28$) [% (*n*/*N*)]	*P* value (Fisher's exact test)
% Achieving major molecular response (MMR)			
With MMR at inclusion	63 % (17/27)	62 % (16/26)	
Achieving MMR out of those without MMR at inclusion	40 % (4/10)	20 % (2/10)	0.63
% Achieving complete cytogenetic response (CCR)[a]			
With CCR at inclusion	78 % (21/27)	69 % (18/26)	
Achieving CCR out of those without CCR at inclusion	60 % (3/5)	75 % (6/8)	1
% Remaining without moderate (≥grade 2) adverse events (AE) of any kind			
Without moderate AEs at inclusion	86 % (24/28)	82 % (23/28)	
Without moderate AEs during the whole study[b]	79 % (19/24)	74 % (17/23)	1
% With clinical concerns[c] *at inclusion and % presenting an improvement*			
With clinical concerns at inclusion	39 % (11/28)	39 % (11/28)	
Presenting an improvement during study	36 % (8/11)	18 % (2/11)	0.64
% With imatinib C_{min} in the target range			
Within 750–1,500 ng/ml at inclusion	39 % (11/28)	46 % (13/28)	
Within 750–1,500 ng/ml at study end	55 % (11/20)	52 % (12/23)	1
Achieving 750–1,500 ng/ml out of those not in interval at inclusion	27 % (3/11)	42 % (5/12)	
>1,000 ng/ml at inclusion	32 % (9/28)	21 % (6/28)	
>1,000 ng/ml at study end	35 % (7/20)	22 % (6/28)	0.50

n/*N* number of patients with event (*n*) out of the total number of patients considered (*N*)

[a] Measured or expected on the basis of the quantitative molecular response measurement

[b] One patient having stopped imatinib in the intervention group because of tolerance problems, but not having presented with grade 2 AEs at the time of the last study visit, was counted as adverse event grade 2, too

[c] Clinical concerns: *at inclusion*: motivation to participate in study efficacy or toxicity concerns or drug–drug interaction, documented suboptimal response or warnings or failure, laboratory grade 3 or clinical grade 2 events; *at study end*: documented suboptimal response or warnings or failure, laboratory grade 3 or clinical grade 2 events during study, treatment discontinuation

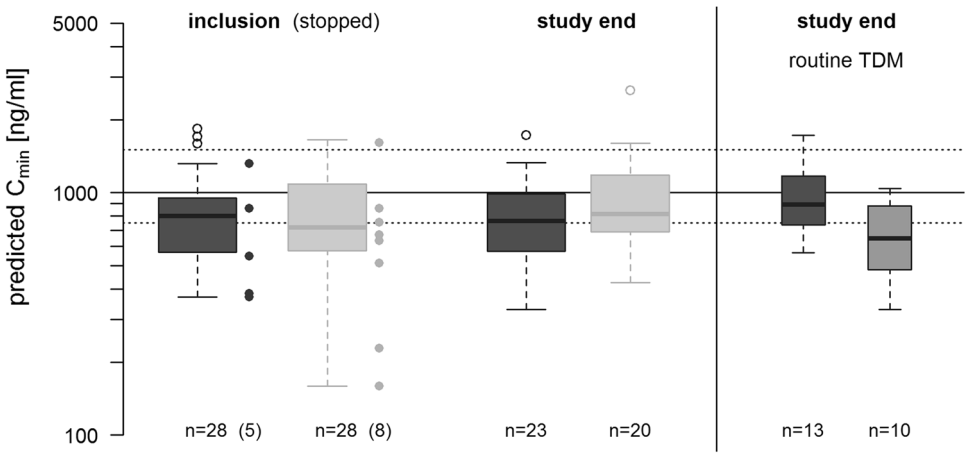

Fig. 4 **a** Predicted imatinib C_{min} at inclusion and at study end in the intervention group (*black boxes* "routine TDM") and the control group (*gray boxes* "rescue TDM"); *dots* represent patients having stopped imatinib treatment. Whiskers extend up to 1.5 times the inter-quartile range. *n* number of patients represented. Median C_{min} (CV %) *Intervention group* inclusion: 802 ng/ml (CV = 44 %), study end: 766 ng/ml (CV = 39 %). *Control group* inclusion: 719 ng/ml (CV = 55 %), study end: 818 ng/ml (CV = 43 %). The eight patients who discontinued imatinib for efficacy concerns had a median C_{min} of 711 ng/ml (CV = 51 %) and the five patients having stopped imatinib for tolerance concerns had a median C_{min} of 384 ng/ml (CV = 84 %); overall median C_{min} 633 ng/ml (41 %). **b** Subgroup analysis in intervention group: patients who received recommended dosage (*dark gray*), median C_{min} (CV %): 895 ng/ml (33 %), versus patients who not or partially received the recommended dosage (*gray*), median C_{min} (CV %): 648 ng/ml (38 %)

was possibly attractive for patients with clinical concerns since it offered TDM free of charge. Second, performing several TDM cycles in "routine TDM" patients may have falsely increased the adverse event rate, since AEs were essentially reported with TDM requests entailing a fluctuation of their grading between mild and moderate in some patients. Notably, more patients in the intervention group were treated with a low imatinib dose at inclusion, suggesting previous tolerance problems.

Consistently, imatinib was mainly discontinued because of AEs in the intervention group (3 out of five patients). Conversely, in the control group, imatinib was mainly discontinued because of efficacy problems (six out of eight patients), whereas MMR, CCR rates and treatment durations were similar at inclusion in both groups. This could indicate that routine TDM mainly prevents treatment failure, while its usefulness for reducing AEs could be limited when targeting C_{min} of 750–1,500 ng/ml in all patients. Among patients not receiving the recommended dosage, 60 % had concentrations below this interval and were partly characterized by a complex condition, resulting in difficulties to apply strict TDM rules. For example, two patients having stopped imatinib for tolerance problems (patient 4–5, Table 4) were not eligible for dosage increase despite low concentrations. In contrast, early TDM may have prevented insufficient efficacy in two young male patients with important body weight, since C_{min} was particularly low under standard doses of imatinib (patient 8 and 12, Table 4). Very low concentrations ($\leq$520 ng/ml) are actually expected in about 25 % of patients on imatinib standard dose and are more likely in corpulent young male patients [18, 34]. In the IRIS study, 25 % of patients with low C_{min} 1 month after treatment start (<650 ng/ml) had lower optimal response rates at 12 and 18 months [19] and a higher discontinuation rate due to unsatisfactory effect.

A systematic review found evidence from observational studies that individual C_{min} *correlates* with treatment outcome in CML patients, especially when considering early therapeutic response [18]. No prospective evaluation of dosage modifications according to individual C_{min} as *pharmacokinetic* marker is, however, available to compare our results. We are only aware of one study being still ongoing (OPTIM, EudraCT: 2010-019568-35). Dosage escalation according to *pharmacodynamic* markers (hematologic and cytogenetic responses) has been reported to induce a response in 40 % of patients and an 89 % progression-free survival at 3 years [35, 36]. In selected imatinib-resistant patients receiving imatinib up to >3 years, the clinical benefit of dosage escalation may be lower [37], suggesting an interest for early escalation. In our study, only 2/11 (18 %) of patients in the routine TDM group reported an improvement of safety or efficacy issues over 1 year (Table 3), with the possible bias of non-adjusted dosage and fluctuating AEs reporting.

Secondary outcomes indicated high response levels in the majority of patients already at inclusion and thus a limited room for improvement: 80 % of patients were in CCR and almost two thirds in MMR, i.e., close to maximal cumulative response rates described [19]. Additionally, patients markedly intolerant to imatinib, in whom rapid treatment discontinuation was preferred to slow dosage readjustment, may have escaped our study. As TDM intervention decreases pharmacokinetic variability, exposure–response associations in this prospective study are expected to be weakened. Still, though not statistically significant, relationships of unbound C_{min} with clinical outcomes were stronger than with total C_{min}. The monitoring of unbound C_{min} could thus receive further consideration in the future, and its usefulness deserves formal evaluation [38]. Pharmacogenetic markers affecting drug transport across cell membranes might additionally be taken into account [39–41].

Based on the individual experience accumulated throughout our study, and despite its limitations mentioned above, we think that TDM can valuably contribute to patient management during imatinib treatment. Measuring imatinib C_{min} 1–3 months after treatment initiation (at best after blood count normalization to decrease pharmacokinetic variability) can provide an individual baseline level of drug exposure and correct gross under- or overexposure. A similar proposal for patients with gastrointestinal stromal tumor treated with imatinib has recently been made [42]. This can later help to evaluate adherence and drug interaction problems and to optimize systemic drug exposure in patients not responding as expected or developing toxic symptoms. It is noteworthy in this respect that the latest treatment recommendations [33] emphasize the importance of managing also low-grade adverse events with attention, to improve quality of life and compliance. This trial was not designed specifically to investigate the benefits of TDM on compliance or drug–drug interaction management—two factors that have been found important for clinical outcomes in CML patients [34, 43]. Further trials are still needed to confirm the possible benefits of TDM in this regard.

Our study highlights both the feasibility and the challenges to prospectively evaluate the benefit of a routine monitoring program for a commercialized drug. The innovative and ethical design of the study, not totally depriving patients from already available TDM in case of concerns, has allowed recruiting a fair number of patients despite the rare indication and the outpatient setting. We suggest to treat the outcome "imatinib discontinuation" separately in future trials, as TDM may actually encourage drug discontinuation in patients intolerant despite acceptable plasma levels. Furthermore, differentiating between efficacy and safety outcomes (possibly also for

Table 4 Characteristics of patients having discontinued imatinib treatment

Ref	G	Characteristics	Treatment duration (months)	Main problem(s) (imatinib dosage during treatment)	C_{min} (ng/ml)	Dose (mg/day)	TDM[c]	Tolerance	Efficacy	Comments
Discontinuation for intolerance mainly										
1	C_r	M, 79 years, 70 kg	4[a]	Intolerance (400 mg)	159	400	Adherence	Dysguesia G2	CHR CCR	Several comorbidities and comedication
2	C_r	F, 48 years, 50 kg	20[a]	Intolerance (400–600 mg) Suboptimal response	1,600	600	500	*Main issue*: Pleural effusion G2/3 (no hospitalization); Several other AEs G1–2 (rash, thrombop., anorexie, edema, anemia, neutrop.)	CCR no MMR	Patient intolerant to other TKIs as well
3	I	M, 46 years, 77 kg	8[a]	Intolerance (200–800 mg)	380	200	400	several AEs G1–2 (anemia, rash, myalgia, headache, nausea, fatigue)	CCR no MMR	
4	I	F, 64 years, 84 kg	24	Intolerance (300–400 mg) (suboptimal response)	545 560 590	400 400 300	Adherence? 600	*Main issue*: G2 rash/pruritus several other AEs G1–2 (myalgia, extrasystolies)	CCR (no MMR % I[b])	
5	I	M, 68 years, 84 kg	7[a]	Intolerance (200–400 mg)	370	200	500	G3 cytotoxicity	MMR	Insertion pb1787
Discontinuation for efficacy concerns mainly										
6	I	M, 77 years, 77 kg	46	Warning (400 mg) (suboptimal response)	860 840	400 400	400 500	G1–2 Sicca syndrome of the eyes	↑BCR-ABL (no MMR % IS[b])	Mutation screening negative
7	C_r	F, 41 years, 67 kg	50[a]	Warning (200–500 mg) (suboptimal response)	670 830 930	400 400 500	500 500 500	–	↑BCR-ABL (no MMR % IS[b])	
8	C	M, 44 years, 112 kg	50	Progression (400 mg)	220	400	800 (2 × 400)	–	No MMR, ↑BCR-ABL, PCyR	Trisomie 8, plus additional abnormalities
9	C_r	M, 78 years, 64 kg	20	Suboptimal response (400–600 mg)	750 1,200 1,190[d]	400 600 500	500 500–600	G1 rash, thrombop., neutrop., anemia	No MMR (CCR expected)	Mutation screening negative, celiac disease
10	I	F, 80 years, 69 kg	14	Failure (400 mg)	1,320	400	400	G1 edema, liver enzymes, anemia	Loss of CCR no MMR	Resistant *ABL* mutation detected several comorbidities
11	C_r	F, 51 years, 92 kg	23	Suboptimal response (400–600 mg) Tolerance problems (600 mg)	630^+ 1,410	400 600	(500–600)	G1–2 edema, fatigue, myalgia, diarrhea	No MMR (CCR expected)	Mutation screening negative
12	C_r	M, 36 years, 92 kg	19	Suboptimal eesponse	510	400	600	G1 fatigue, G2 liver enzymes	No MMR (CCR expected)	

Table 4 continued

Ref	G	Characteristics	Treatment duration (months)	Main problem(s) (imatinib dosage during treatment)	C_{min} (ng/ml)	Dose (mg/day)	TDM[c]	Tolerance	Efficacy	Comments
13	C_r	M, 79 years, 99 kg	13	Warning (400 mg) (suboptimal response)	860	400	–	G1 edema	No MMR (no CCR expected)	mBCR-ABL p190

Ref, reference number of patient; G, allocated group; I, intervention group with routine TDM; C, control group; C_r control group having requested "rescue" TDM

[a] With treatment interruptions and/or dose reductions due to (initial) tolerance problems

[b] no MMR % IS: retrospectively, patients did not have MMR on international scale (IS). Before standardization of laboratory results, the response had been interpreted as MMR, however

TDM[c] : recommended dosage for achieving target range; increase only suggested if tolerance improved and dosage decrease only if efficacy acceptable

[d] Sampling less than 4 h after last drug intake → C_{min} estimate may be imprecise

target plasma levels), restricting the inclusion to a treatment naïve patient population and investigating reasons for prescribers' non-adherence to dosage recommendations would probably improve the design and power to evaluate the impact of TDM on patient's outcomes. Such trial design could thus represent an interesting framework to develop similar, larger studies for many newer anticancer agents [15, 23, 24, 44]. International multicenter collaborations will probably be needed to recruit appropriate numbers of patients.

In conclusion, while this first prospective target concentration intervention trial could not formally demonstrate a benefit of "routine TDM" of imatinib, especially due to a small patient number and limited prescriber's adherence to dosage recommendations, we observed that the patients actually applied the advised dosages more often met the target concentrations and the combined outcome (efficacy, tolerance and persistence). A cycle of routine TDM could thus be favorable in patients *eligible* to dosage adjustment.

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