Original Research

Relationship between imatinib trough concentration and outcomes in the treatment of advanced gastrointestinal stromal tumours in a real-life setting

Stéphane Bouchet a,b,c,l, Sylvie Poulette a,l, Karine Titier a,b,c, Nicholas Moore a,b,c, Régis Lassalle a,d, Abdelilah Abouelfath a,d, Antoine Italiano e, Christine Chevreau f, Emmanuelle Bompas g, Olivier Collard h, Florence Duffaud i,j, Maria Rios k, Didier Cupissol l, Antoine Adenis m, Isabelle Ray-Coquard n,o, Olivier Bouché p, Axel Le Cesne q, Binh Bui e, Jean-Yves Blay n,o, Mathieu Molimard a,b,c,*

a Univ. de Bordeaux, Bordeaux, F-33000, France
b INSERM, U1219, Bordeaux, F-33000, France
c CHU de Bordeaux, Bordeaux, F-33000, France
d INSERM CIC Bordeaux CIC3401 Pharmaco-épidemiologie, Bordeaux, F-33000, France
e Institut Bergonie, Bordeaux, F-33000, France
f Institut Universitaire du Cancer Toulouse – Oncopole, Toulouse, F-31300, France
g Centre René Gauducheau, Nantes (Saint-Herblain), F-44805, France
h Institut de Cancérologie Lucien Neuwirth, Saint Priest-en-Jarez, F-42270, France
i CHU La Timone, Marseille, F-13385, France
j Aix Marseille Université (AMU), France
k Institut de Cancérologie de Lorraine – Alexis Vautrin, Nancy, F-54500, France
l Centre Val d ’Aurelle, Montpellier, F-34298, France
m Centre Oscar Lambret, Lille, F-59020, France
n Centre Léon Bérard, Lyon, F-69008, France
o Université Claude Bernard Lyon 1, France
p CHU Robert Debré, Reims, F-51092, France
q Institut Gustave-Roussy, Villejuif, F-94805, France

Received 23 December 2015; accepted 30 December 2015
Available online 4 February 2016

* Corresponding author: Département de Pharmacologie, CHU de Bordeaux — Université de Bordeaux — INSERM U1219, 33076 Bordeaux Cedex, France. Tel.: +33 (0)5 57 57 15 60; fax: +33 (0)5 57 57 46 71.
E-mail address: mathieu.molimard@u-bordeaux.fr (M. Molimard).
1 Co first author.

http://dx.doi.org/10.1016/j.ejca.2015.12.029
0959-8049/© 2016 Elsevier Ltd. All rights reserved.
1. Introduction

Gastrointestinal stromal tumours (GISTs) are the most common sarcoma (mesenchymal tumours) of the gastrointestinal tract. Approximately 60% of these occur in the stomach, 30% in the small bowel, 5% in the colon and rectum, and 5% in the oesophagus [1]. Prognosis evaluation in GIST is currently based on tumour diameter, mitotic count and anatomic localisation [2].

Recent studies have also shown that primary site localisation should be considered as an independent risk factor [3,4]. Most GISTs show mutations in KIT or platelet-derived growth factor receptor alpha [5,6] that are targeted by the selective tyrosine kinase inhibitor imatinib mesylate (Glivec™, Novartis Pharmaceuticals). This molecule used as frontline therapy has dramatically improved the prognosis of patients with advanced GIST. In imatinib-treated patients it has been reported that 80% obtained clinical response [7] and that median survival was extended by nearly four times the historic values from the pre-imatinib era [8].

To improve imatinib treatment efficacy, dose-escalation has been investigated, and it was found that it could overcome imatinib failure, especially for patients with KIT exon 9 mutation [9,10]. These studies did not however investigate any relationship between this and plasma levels, even if pharmacokinetic studies have found a correlation between steady state trough imatinib plasma concentrations (Cmin) and efficacy. In chronic myeloid leukaemia (CML), a threshold of 1000 ng/ml has been significantly associated with better cytogenetic and molecular responses [11–13]. For GIST it has been reported in a clinical trial that patients with Cmin at 1 month below the first quartile of concentration values (1110 ng/ml) had shorter time to progression than patients in other quartiles [14]. This cannot preclude that the threshold of imatinib Cmin in GIST is lower than this concentration. A more recent study indicated that imatinib Cmin fall down of about 30% over the first 3 months of treatment [15], showing up that the proposed value determined at 1 month should not be used during all the follow-up. These studies also underline that dose cannot predict plasma levels owing to high inter-patient variability [12,14], which depends on numerous individual pharmacokinetics parameters including CYP polymorphisms, drug transporters such as P-glycoprotein, protein binding and drug-drug interactions [16–18]. For gastric GIST patients, this is further complicated by surgery, those having undergone partial or total gastrectomy being reported to have significant lower Cmin than those who had not [19]. Taken together these studies on the pharmacokinetics and efficacy of treatment suggest that therapeutic drug monitoring (TDM) could be a useful tool for individual treatment management and optimisation. In advanced GIST, a Cmin threshold that could serve as reference to guide TDM in clinical practice remains to be defined.

The initial observations of a relationship between duration of treatment and concentrations in GIST
patients showed that long-term survivors tended to have higher imatinib plasma levels compared with those who had more recently initiated treatment [20,21]. Thus, the relationship between Cmin, progression-free survival (PFS) and clinicopathological factors in patients who benefit from the plasma level testing service was prospectively studied. The main objective of this study was to investigate whether an imatinib Cmin value would predict for the risk of progression in advanced GIST could be defined in real-life setting conditions.

2. Patients and methods

2.1. Patient inclusion

The University of Bordeaux centre offers physicians the possibility to monitor imatinib plasma concentration of their GIST and CML patients receiving this treatment. A cohort was identified from unresectable or metastatic evaluable GIST patients of 23 centres who benefited from imatinib plasma level testing. Patients considered for this cohort had to be treated with imatinib 400 mg/d from initiation until last reported event and to have at least one trough imatinib concentration determination after a minimum of 3 months of treatment (steady state according to Eechoute et al. [15]) and before time of first progression.

2.2. Measurement of imatinib concentrations

Physicians submitting plasma samples for plasma level testing were asked to draw the blood sample just before an imatinib dose (generally 24 ± 3 h following the previous dose) into a heparinised vial. Samples were centrifuged at 3000 g for 5 min. Supernatants were then shipped to the Bordeaux centre at ambient temperature (<30 °C) using an approved carrier. Imatinib plasma concentrations were determined using liquid chromatography coupled to electrospray-ionisation tandem mass spectrometry, as previously described [22]. The lower limit of quantification is 10 ng/ml.

2.3. Data collection

Physicians submitting samples were required to complete a form that collected information including: details of the time elapsed between last intake of imatinib and drawing of blood (to confirm trough sampling); reason(s) for requesting imatinib BLT; dose and duration of imatinib treatment; primary tumour site; metastasis localisation(s); tumour surgery; response to treatment, stable disease, or progression (and date) according to RECIST (Response Evaluation Criteria In Solid Tumors) criteria; mutational status if available. Follow-up was considered as the duration of treatment under imatinib. This observational study was approved by the institutional committees in charge of data protection in biomedical research in France (CCTIRS, CNIL). According to their requirements, an information sheet was provided to patients for informed consent. All data were recorded in an approved clinical database constructed prospectively using FileMaker® software (FileMaker, Inc., version 9, CA, United States of America [USA]).

2.4. Statistical methods

Descriptive results are presented in terms of mean, standard deviation (SD), median and quartiles for quantitative data, and in terms of proportion for qualitative data. First trough samples at steady state (taken after at least 1 month of treatment) were used to determine Cmin values. Patients were identified at the first Cmin determination and the time to first Cmin was determined from initiation of imatinib treatment. Kaplan–Meier estimator was used to estimate overall PFS in this cohort. Patients who had discontinued treatment or died without progression were censored. Discrimination between progression and non-progression, which was described to be a viable predictor parameter of imatinib-treated GIST outcome, was used to evaluate effectiveness of imatinib treatment [23]. For each concentration decile, the relative PFS of patients above and below this was investigated using the log-rank test method, as previously described for pazopanib in renal cell carcinoma [24]. Cmin threshold was defined as the first lower concentration decile boundary that had the most significant relative PFS difference. A Cox proportional hazard regression was performed to assess factors associated with longer PFS; stratification on the time to first Cmin (<1 year, 1–2 years and >2 years) allowed to take into account the effect of this variable in the calculation of relative risk by the model. All analyses were performed using the SAS® software (SAS Institute, version 9.2, NC, USA).

3. Results

3.1. Patient and treatment characteristics

Among the 220 patients with advanced GIST, 96 patients treated with imatinib at 400 mg/d and fulfilling all inclusion criteria were evaluated. The median age was 62 years (range: 37–81) at the initiation of imatinib with a sex ratio of 1.4 (42% were female). Patients had median time to first Cmin of 15.2 months (range 3.1–99.5), and they were followed for a median duration of 27 months (range: 3.8–107.5, Table 1). Reported localisations of GIST were stomach (n = 41), small bowel (n = 34), colorectal (n = 8), and other (n = 13): oesophageal (n = 1), mesenteric (n = 4), rectovaginal (n = 2), anal (n = 1), pelvic (n = 1) and difficult to locate (n = 4). Data regarding mutations were available for 47 patients,
and KIT exon 11 mutation accounted for 70% of these (Table 1).

3.2. Distribution of trough plasma concentrations

Mean (±SD) Cmin was 868 (±536) ng/ml, and inter-individual coefficient of variation was 75%. For patients with at least two Cmin determinations, there was an intra-individual coefficient of variation of 26% (n = 48). For those with stomach GIST localisation mean (±SD) Cmin was 793 (±535) ng/ml and for those with small bowel localisation this was 998 (±623) ng/ml; these did not differ statistically (Table 2).

3.3. Impact of localisation on outcomes

Using Kaplan–Meier, median PFS estimated for included patients (n = 96) was 96.0 months (Fig. 1), and the 25 patients who progressed did so after a median of 21.4 months (Table 2). Median PFS for stomach GIST patients was not reached at 9 years while median PFS for small bowel GIST patients was achieved at 67.4 months. The progression rate was three times higher for small bowel than stomach GISTs (38% versus 12% during the follow-up; Table 2). Estimated PFS for stomach and small bowel localisations were significantly different (p < 0.0037). GIST, gastrointestinal stromal tumour.

Concerning those with stomach GIST for whom data regarding surgery were reported, the 20 patients with partial or total tumour resection had significantly lower mean Cmin than the 19 without resection (respectively 530 (±295) and 1020 (±626) ng/ml; p = 0.02). For those with small bowel GIST such a difference was not observed.

### Table 1
Characteristics of the patients.

<table>
<thead>
<tr>
<th></th>
<th>Included patients (n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at initiation, years</td>
<td>Mean (±SD) 62 (±12)</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>1.4 (56/40)</td>
</tr>
<tr>
<td>Localisation, n (%)</td>
<td>Stomach 41 (43)</td>
</tr>
<tr>
<td></td>
<td>Small bowel 34 (35)</td>
</tr>
<tr>
<td></td>
<td>Colorectal 8 (8)</td>
</tr>
<tr>
<td></td>
<td>Others 13 (14)</td>
</tr>
<tr>
<td>Mutation, n (% of reported)</td>
<td>KIT Exon 11 33 (70)</td>
</tr>
<tr>
<td></td>
<td>KIT Exon 9 5 (11)</td>
</tr>
<tr>
<td></td>
<td>Wild type KIT 3 (6)</td>
</tr>
<tr>
<td></td>
<td>Others 6 (12)</td>
</tr>
<tr>
<td></td>
<td>Unreported 49</td>
</tr>
</tbody>
</table>

SD, standard deviation.

### Table 2
Cmin, coefficients of variation and response according to localisation.

<table>
<thead>
<tr>
<th></th>
<th>Any site (n = 96)</th>
<th>Stomach (n = 41)</th>
<th>Small Bowel (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration, ng/ml</td>
<td>Mean (±SD) 868 (±536)</td>
<td>793 (±535)</td>
<td>998 (±623) NS</td>
</tr>
<tr>
<td></td>
<td>Median 756</td>
<td>658</td>
<td>893 NS</td>
</tr>
<tr>
<td></td>
<td>Interquartile range [25–75%] [460–1116]</td>
<td>[385–1065]</td>
<td>[625–1265]</td>
</tr>
<tr>
<td>Coefficient of variation, %</td>
<td>Intergroup 75</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Intragroup 26 NS</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Evolution of patients disease/treatment</td>
<td>Disease control, n (%)</td>
<td>64 (67)</td>
<td>33 (81)</td>
</tr>
<tr>
<td></td>
<td>Progression, n (%)</td>
<td>25 (26)</td>
<td>5 (12)</td>
</tr>
<tr>
<td></td>
<td>Mean time from initiation to progression (±SD)</td>
<td>30 (±21)</td>
<td>35 (±18)</td>
</tr>
<tr>
<td></td>
<td>Median time from initiation to progression</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Treatment discontinuation, n (%)</td>
<td>4 (4)</td>
<td>3 (7)</td>
</tr>
<tr>
<td></td>
<td>Death without progression, n (%)</td>
<td>3 (3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

SD, standard deviation; NS: not significant (stomach versus small bowel); p > 0.05.

Time from initiation to progression measured for patients who experienced progression.

a n = 48.
b Disease control = complete or partial response + stable disease.
different (p = 0.0037, log-rank test; Fig. 1); at 5 years, 75% of stomach GISTs (95% confidence interval [CI]: 46–90%) did not experience progression whereas for those with small bowel GIST, PFS progression was not reached in 54% of cases (95% CI: 31–72%).

3.4. Relationship between trough plasma concentration and PFS

With regards to the first Cmin, the decile that produced the most statistically significant difference in PFS was 760 ng/ml in the whole population (p = 0.0256, log-rank test; Fig. 2A) with a trend for 900 and 1020 ng/ml (p = 0.1361 and 0.0556 respectively). The 1110 value, quartile found by Demetri et al. was not significantly applied to the specific patient population (p = 0.1107). Median PFS for patients with Cmin below the 760 ng/ml threshold was 56 months, while median PFS was not reached for patients with Cmin above this threshold (Fig. 2B). For the 900 ng/ml decile, this was 56 and 96 months respectively and for 1020 ng/ml decile and 1110 value, this was 67 months and unreached.

Separate log-rank tests on stomach and small bowel GISTs also found a Cmin threshold of 760 ng/ml Cmin above this threshold induced significantly longer PFS for the stomach (p = 0.043, Fig. 3A) and small bowel GIST (p = 0.049, Fig. 3B). At 5 years, no stomach GIST patients with Cmin above this threshold experienced progression, whereas 45% (95% CI: 18–84%) for those with Cmin below this threshold did so. In patients with small bowel GIST, estimated PFS rates at 5 years were 74% (95% CI: 44–90%) in those with Cmin above the threshold, and 26% (95% CI: 4–56%) in those with lower Cmin.

3.5. Multivariate analysis of factors associated with PFS

Multivariate Cox regression analysis found that small bowel localisation was associated with an increased relative risk of progression of 3.09 (95% CI: 1.03–9.31)

Fig. 2. Relationship between trough plasma concentration and progression-free survival (PFS). (A) Association of imatinib Cmin thresholds with PFS. (B) PFS according to the 760 ng/ml threshold imatinib Cmin in the whole population. Median PFS for patients with Cmin below 760 ng/ml was 56 months, but was not reached for patients with Cmin above 760 ng/ml. Difference of PFS between patients with Cmin above and below this threshold was significant (p = 0.0256). (C) PFS according to the 1110 ng/ml imatinib Cmin value found by Demetri et al. in the whole population. Median PFS for patients with Cmin below 1110 ng/ml was 67 months, but was not reached for patients with Cmin above 1110 ng/ml. Difference of PFS between patients with Cmin above and below this threshold was not significant (p = 0.1107).

Fig. 3. Progression-free survival (PFS) according to the 760 ng/ml threshold imatinib Cmin for stomach (A) or small bowel (B) GIST patients. (A) Median PFS was not reached for stomach GIST patients with Cmin below or above 760 ng/ml. Difference of PFS between stomach GIST patients above and below this threshold was significant (p = 0.0435). (B) Median PFS for small bowel GIST patients with Cmin below 760 ng/ml and for patients above 760 ng/ml this was 96 months respectively. Difference of PFS between small bowel GIST patients above and below threshold was significant (p = 0.0493). GIST, gastrointestinal stromal tumour.
Table 3
Prognostic factors of progression experience under imatinib treatment: multivariate Cox regression analysis after included stratification on the time between initiation and first Cmin (<1 year; [1–2 years] ≥ 2 years), n = 96.

<table>
<thead>
<tr>
<th></th>
<th>Progression</th>
<th>Multivariate regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 71)</td>
<td>Yes (n = 25)</td>
</tr>
<tr>
<td>Primary tumour site, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>36 (50)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Small bowel</td>
<td>21 (30)</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Other localisations</td>
<td>14 (20)</td>
<td>7 (28)</td>
</tr>
<tr>
<td>Imatinib concentration threshold, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥760 ng/ml</td>
<td>40 (56)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>&lt;760 ng/ml</td>
<td>31 (44)</td>
<td>17 (68)</td>
</tr>
</tbody>
</table>

CI, confidence interval; RR: relative risk.

versus stomach localisation (p = 0.0255), and that patients with a first Cmin below the threshold of 760 ng/ml had a relative risk of progression of 2.87 (95% CI: 1.13–7.32) of progression (p = 0.0271; Table 3).

4. Discussion

TDM for GIST patients treated with imatinib is routinely performed in real-life practice. One aspect of TDM is efficacy that requires a target threshold value and current data indicate that this is probably somewhere below the quartile of 1100 ng/ml found by Demetri et al. [14,15]. The current report explores this further, using real-life TDM of GIST patients, and although a trend was found not far (1020 ng/ml), the most significant Cmin value associated with reduced risk of progression was as low as 760 ng/ml.

In the present study, mean Cmin of GIST patients (868 ng/ml) appeared to be in the lower range of previously reported values (from 900 to 1215 ng/ml) [11,12,25–27]. A higher mean Cmin was observed by Demetri et al.[14] and this could explain why the quartile analysis performed in their study could not have found value lower than 1100 ng/ml. The difference between Cmin could be related to the observation of Judson et al. and Eechoute et al., showing that Cmin could decrease over the first 3 months of treatment, from 100% of ‘bioavailability’ to 70% [15,18]. One of the hypotheses is the decrease of inflammation within these 3 months. After this period, the decrease was no more observed among the patients of the studied cohort (nor those of the Bordeaux database) throughout the first year of treatment. The residual observed variations could be attributed to a large inter- and intra-individual variability. Herein was reported a high inter-patient Cmin variability, which is in-line with previous studies [11–14,18,19]. Such variation is attributable to a number of factors [16–18] and is further compounded and probably increased in observational studies by the issue of compliance, or more precisely, lack thereof [25]. In addition to this, imatinib concentration of GIST patients is complicated by factors associated with localisation. For instance, gastrectomy impacts on absorption and thus imatinib plasma concentrations [19]. These aspects are reflected in the results of the present study, as GIST patients who had undergone gastrectomy had significantly lower Cmin than those not having had surgery, which resulted in a trend for patients with stomach GIST to have lower Cmin values (median = 658 ng/ml) than those with small bowel GIST (median = 893 ng/ml). Independently of imatinib treatment, GIST patients also differ in their underlying risk as small bowel GISTs behave more aggressively than those of the stomach. The gastric GIST patients should probably be considered as a particular subpopulation regarding the dose-concentration relationship, whereas small bowel GISTs’ median value is very close to that of CML patients (median = 896 ng/ml in [13]). Another point regards the finding of the same threshold for both stomach and small bowel localisations. This indicates that higher concentrations would not have been resulted in greater effectiveness in either subpopulation treated with imatinib 400 mg/d. However, at 5 years none of those with stomach GIST and plasma imatinib level above the threshold experienced progression whereas one quarter of those with small bowel GIST did so. Taken together, this may reflect the difference in underlying risk associated with small bowel GIST.

As often happens, the real-life setting could have introduced several limitations to this study: notably patient selection bias, through the selection of patients who receiving 400 mg/d throughout their treatment, and secondly through selection of patients who had not progressed before Cmin determination. The first point is of lesser concern as such patients’ regimen represent 92% of GIST patients included in the TDM database (personal observation) although this may not be completely representative of the situation in France. The second point resulted in patients being included after a median of 15 months following treatment initiation and led to an apparent prolonged PFS compared to clinical trials due to an immortal time bias (i.e. time to first Cmin). This was addressed by stratification on time to
first Cmin in the multivariate Cox regression analysis; however those who experienced progression did so after a median of 21.4 months, which is consistent with usual clinical observations [1]. Such patient selection does not affect the representativeness of the study with respect to real-life TDM. Furthermore, the method used to determine the threshold was based on the relative difference of PFS, which was not to be affected by the immortal time bias.

In conclusion, the threshold of 760 ng/ml imatinib Cmin is associated with a longer PFS in advanced GIST whatever the location of the primitive tumour. Definition of this threshold could help physicians in case of poor response to treatment and is the first step leading to TDM justification. Further studies measuring the impact of dose adjustments to insure concentration above this threshold are required to definitively justify TDM of imatinib in advanced GIST patients.

Disclosure

Disclosure in the field of GIST.

A Adenis: Speaker (Novartis, Bayer, Pfizer), Research funding (Bayer)

JY Blay: Consultancies (Novartis, GlaxoSmithKline, Roche, PharmaMAR, MSD), Research Funding (Novartis, GlaxoSmithKline, Roche, PharmaMAR MSD).

O Bouché: Consultancies (Roche) Speaker (Novartis, Amgen)

F Duffaud: Consultancies (Lilly, Bayer, Pharma-MAR) Speaker (Bayer)

A Le Cesne: Consultancies (Pfizer, PharmaMAR, Novartis).

O Collard: Consultancies (Novartis), Speaker (Bayer).

M Molimard: Speaker (Novartis).

Funding

This study was supported for shipment and analysis of blood samples by Novartis Pharmaceuticals France. No specific funding existed for the substudy reported in this paper. There was no role of the funding source in the preparation of the manuscript.

Conflict of interest statement

All other authors declare no conflict of interest.

Acknowledgements

The authors thank Philip Robinson for his great help and support in manuscript preparation.

References


