Letter to the Editor

Imatinib plasma levels: correlation with clinical benefit in GIST patients

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Published online 23 February 2010

Sir,

The issue of suitability of therapeutic drug monitoring (TDM) for imatinib continues to fuel controversies. Unlike two previous studies in gastrointestinal stromal tumours (GIST) patients (Judson et al., 2005; Delbaldo et al., 2006), a recent clinical pharmacokinetic (PK) substudy carried out on the basis of the B2222 trial, evaluating imatinib in patients with unresectable or metastatic CD117-positive GIST, found a correlation between imatinib total exposure and clinical response. Trough levels over 1100 ng ml\(^{-1}\) predicted a better overall benefit rate (composite clinical outcome; Demetri et al., 2009). These results are thus in line with observations made in CML patients, showing trough levels over 1000 ng ml\(^{-1}\) to predict a better molecular response rate (Picard et al., 2007; Larson et al., 2008).

These concentration–effect relationships confirm and strengthen our results obtained in a population of GIST patients, albeit smaller-sized (38 patients), which we had previously reported in the Journal (Widmer et al., 2008). We have indeed observed that higher free imatinib exposure predicts a higher probability of therapeutic response, when taking into account tumour KIT genotype. The strongest association was observed in patients harbouring exon 9 mutation or wild-type (wt) KIT, which is known to decrease tumour sensitivity towards imatinib (Heinrich et al., 2003). In fact, we found that, in our population of patients, free plasma concentration (the pharmacologically active species in plasma; i.e., imatinib fraction not bound to $\alpha$-acid glycoprotein (AGP); Widmer et al., 2006) was a better predictor of the clinical response rather than total concentration. This free exposure was derived from the total exposure using a mathematical model taking into account the AGP plasma level (Widmer et al., 2006). Moreover, we found a significant relationship between this free exposure and clinical response only in patients with exon 9 mutation and wt KIT. Of importance, we also observed significant correlations between total, as well as free, imatinib exposure and the occurrence of side effects (Widmer et al., 2008).

To better compare our results with those of the B2222 PK substudy, we recomputed maximum a posteriori extrapolations for both total $C_{\text{min}}$ and free $C_{\text{min}}$ in our patient samples, rather than considering the global imatinib exposure (area under the plasma concentration–time curve) that was previously analysed (Widmer et al., 2008). Among the 38 GIST patients of the previous analysis, AGP plasma levels – required to calculate free $C_{\text{min}}$ – were available for 36 patients. All these patients were included in an observational study approved by the Ethics Committee of the Lausanne Faculty of Medicine. Informed written consent was obtained from all the participants. A specific population PK model (Widmer et al., 2006) was used for this extrapolation (using NONMEM, version VI 2.0, NONMEM Project Group, University of California at San Francisco, San Francisco, CA, USA). We investigated their correlation with clinical benefit, defined as response evaluation criteria in solid tumours (RECIST) complete response, partial response or stable disease, by logistic regression analysis (using Stata version 10.1, Stata Co., College Station, TX, USA).

We found no significant overall association between total $C_{\text{min}}$ and response in our GIST population. Conversely, imatinib free $C_{\text{min}}$ was correlated with a clinical benefit, with responders having higher free levels than non-responders (RECIST progressive disease). This relationship did not reach significance over the whole patient sample series (i.e., irrespective of the KIT genetic profile; area under the ROC curve $= 0.594$ and $P = 0.26$ using logistic regression analysis on log, values of free $C_{\text{min}}$). However, focusing on exon 9 mutated and wt KIT cases allowed the identification of a clear relationship (area under the ROC curve $= 0.932$ and $P = 0.013$). The cutoff value of 20 ng ml\(^{-1}\) free imatinib plasma trough level corresponded to the best sensitivity (86%) and specificity (100%). The geometric average estimate of imatinib free fraction across our study samples was 1.0% (CV 45%). The mean daily doses of imatinib only tended to be slightly higher in exon 9 or wt KIT patients compared with exon 11 KIT patients (649 mg vs 590 mg daily, respectively; $P = 0.07$ using t-test). Table 1 describes our GIST patient samples and Figure 1 shows the striking difference between the free $C_{\text{min}}$ values of responder and non-responder exon 9 or wt KIT patients (per-sample analysis).

This per-sample analysis was performed because imatinib doses administered to each patient during the course of this 3-year-long observational study could be increased or decreased. The concentration, and possibly the response or adverse events related to treatment, may therefore vary at some point for a given patient. Interestingly, a similar analysis carried out on a per-patient basis (i.e., expressing only a single mean free $C_{\text{min}}$ and one median response for each individual patient) provided a similar relation-
ship and cut-off, however, reaching statistical significance because of the limited number of patients with exon 9 or wt KIT. The results from our observational study should therefore still be considered cautiously and will have to be confirmed in a larger study and cut-off, without, however, reaching statistical significance because of the limited number of patients with exon 9 or wt KIT. The results from our observational study should therefore still be considered cautiously and will have to be confirmed in a larger study.

Table I

| RECIST response          | All patients (wt, exon 9 and exon 11 KIT) | Exon 9 and wt KIT patients |
|--------------------------|------------------------------------------|---------------------------|
|                          | n (blood samples)                        | Median free $C_{\min}$ and range (ng ml$^{-1}$) | n (blood samples) | Median free $C_{\min}$ and range (ng ml$^{-1}$) |
| Progressive disease     | 50                                       | 13.4 (3.8–22.9)           | 19               | 10.1 (6.1–17.4) |
| Stable disease          | 63                                       | 15.8 (4.5–39.3)           | 4                | 19.9 (13.7–20.2) |
| Partial response        | 72                                       | 13.3 (2.8–33.0)           | 2                | 20.5 (14.9–26.1) |
| Complete response       | 8                                        | 26.0 (25.0–27.0)          | 8                | 26.0 (25.0–27.0) |

Abbreviations: AGP = α1-acid glycoprotein; GIST = gastrointestinal stromal tumour; RECIST, response evaluation criteria in solid tumours. Each patient provided between 1 and 12 samples over 3 years (median: 4 samples per patient), along with current RECIST response status.

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British Journal of Cancer (2010) 102(7), 1198–1199