Barratt DT, Cox HK, Menelaou A, Yeung DT, White DL, Hughes TP, Somogyi AA. CYP2C8 genotype significantly alters imatinib metabolism in chronic myeloid leukaemia patients. Clinical Pharmacokinetics.

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Electronic Supplementary Material 3: Dose and day effects on steady-state trough plasma imatinib concentrations in chronic myeloid leukaemia patients.

Methodology

The dose proportionality of trough plasma imatinib concentrations within patients decreasing to 400 mg/day, and increasing to 800 mg/day, from 600 mg/day before day 90 of treatment was determined separately by linear mixed effects modelling (patient ID as random effect) of the log transformation of the power regression model: $\log_e(\text{trough plasma imatinib concentration}) = \beta \cdot \log_e(\text{dose}) + \alpha + \epsilon$. Dose proportionality was concluded to exist if the 90% confidence interval for the slope estimate ($\beta$) included the value of 1.0.

Results

Plasma imatinib concentrations were a median 52% higher at 600 compared to 400 mg/day, and 149% higher at 800 compared to 600 mg/day (Fig. S1). Changes in plasma imatinib concentrations were variable, but approximately dose-proportional in patients decreasing from 600 to 400 mg/day before day 90 (Fig. S2); $\beta$ (90% confidence interval) = 1.0 (0.3 to 1.7). Changes in trough plasma imatinib concentrations were greater than dose proportional in patients increasing from 600 to 800 mg/day before day 90 (Fig. S2); $\beta$ (90% confidence interval) = 3.1 (2.7 to 3.5). Estimates of $\beta$ were similar between CYP2C8*1/*1 [3.0 (2.5 to 3.4)] and CYP2C8*3 carrier [3.8 (2.9 to 4.6)] patients who dose increased to 800 mg/day. Fig. S2 shows log$_e$-transformed power model regression best fit and dose-normalised plasma imatinib concentrations for patients with dose changes between days 22 and 90 of treatment.
**Fig. S1** Dose and day effects on trough total plasma imatinib and N-desmethyl imatinib concentrations in CML patients (a) maintained on 600 mg/day, (b) with dose reduced to 400 mg/day between days 22 and 90, and (c) with dose increased to 800 mg/day between days 22 and 90. Black boxes and filled circles are plasma imatinib concentrations, and grey boxes and open circles are plasma NDIM concentrations. Box plot bars are median, 25th and 75th percentiles, minimum and maximum. Circles represent individual paired data connected by solid (imatinib) or dashed (NDIM) lines.

**Fig. S2** Dose-proportionality of trough plasma imatinib concentrations in CML patients decreasing to 400 mg/day, or increasing to 800 mg/day, from 600 mg/day before day 90 of treatment. (a) Best fit (solid black lines) and 95% confidence interval (dotted black lines) of log$_e$-transformed power regression model $\log_e(\text{trough plasma imatinib concentration}) = \beta \cdot \log_e(\text{dose}) + \alpha + \varepsilon$ compared to $\beta = 1$ (dashed grey lines). Trough plasma imatinib (black circles) and NDIM (open circles) concentrations normalised to 600 mg/day for patients (b) reducing to 400 mg/day, or (c) increasing to 800 mg/day, prior to day 90. Circles represent individual paired data connected by solid (imatinib) or dashed (NDIM) lines.
Discussion

Whilst imatinib exposure has previously been reported as dose-proportional up to 1000 mg/day, this is with split dosing (twice a day) for doses 800 mg/day and above [1, 2]. The only other study to report on the dose-trough plasma imatinib concentration relationship for 800 mg/day once daily also indicated a greater than dose-proportional increase from 400 mg/day [3]. Further studies would be required to test a hypothesis that the lower metabolic ratio and non-dose proportionality at 800 mg/day and above are the result of dose-dependent mechanism-based CYP3A4 inhibition [4], although this may be unlikely since steady-state plasma imatinib concentrations and NDIM/imatinib ratio were recently shown to be unrelated to variable CYP3A activity (quinine 3-hydroxylation) in CML patients [5].

Analysis of only 2 doses and using trough concentrations (instead of AUC for example), is not generally a good test of dose-proportionality. However, deviation from the expected proportional dose-plasma concentration relationship between 600 and 800 mg/day is obvious (Fig. S2). Combining all patients, or those with dose changes (up and down), in linear mixed effects analyses covering all three doses would not have been appropriate in this study because no patients received all three doses, and there was apparent dose-proportionality from 400 to 600 mg/day, making a linear fit of the loge-transformed power model from 400-800 mg/day inappropriate.

References