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ORIGINAL ARTICLE

Monte Carlo simulations of the clinical benefits from therapeutic drug monitoring of sunitinib in patients with gastrointestinal stromal tumours

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Abstract
Purpose Therapeutic drug monitoring (TDM) is being considered as a tool to individualise sunitinib treatment of gastrointestinal stromal tumours (GIST). Here, we used computer simulations to assess the expected impact of sunitinib TDM on the clinical outcome of patients with GIST.
Methods Monte Carlo simulations were performed in R, based on previously published pharmacokinetic–pharmacodynamic models. Clinical trials with dose-limiting toxicity and patient dropout were simulated to establish the study size required to obtain sufficient statistical power for comparison of TDM-guided and fixed dosing.
Results The simulations revealed that TDM might increase time to tumour progression by about 1–2 months (15–31 %) in eligible patients. However, the number of subjects required for a sufficient statistical power to quantify clinical benefit of TDM guided is likely to be prohibitively high (>1000).
Conclusion Although data from randomised clinical trials on the clinical impact of sunitinib TDM are lacking, our findings support implementation of sunitinib TDM in clinical practice. For rare cancers with well-defined exposure–response relationships, modelling and simulation might allow the optimisation of dosing strategies when clinical trials cannot be performed due to low number of patients.

Keywords Sunitinib · Therapeutic drug monitoring · Monte Carlo simulation · Individualised medicine · Gastrointestinal stromal tumours

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Introduction

The multi-kinase inhibitor sunitinib (Sutent®) is indicated for the treatment of renal cell carcinoma, imatinib-resistant or imatinib-intolerant gastrointestinal stromal tumours (GIST) and pancreatic neuroendocrine tumours [1]. Like most other targeted chemotherapy agents, sunitinib is recommended to be prescribed at a fixed dose, regardless of patient characteristics like weight and body surface area [2]. Despite this fixed dose, interindividual variability in drug exposure is high (±30 %) [3–5]. Low sunitinib exposure is associated with reduced response rate, time to tumour progression and overall survival [6]. It has been recommended that dose increases should be undertaken in patients with a total trough level (TTL) of sunitinib and its primary active metabolite SU12262 below 50 ng ml^{-1} [2, 7]. This is particularly relevant considering that the target TTL of 50 ng ml^{-1} is obtained only by about half of the patients on the fixed-dose regimen [3, 7].

There are many different sources of pharmacokinetic variability for sunitinib, making a priori prediction of an individual patient's TTL (and subsequent individualisation of sunitinib dose) challenging [4, 7]. Therapeutic drug monitoring (TDM), the measurement and interpretation of drug or metabolite concentrations in patient samples, has been suggested as a potential strategy to guide sunitinib dosing. Recently, sunitinib TDM appeared to successfully

guide dose titration towards target TTL in patients that tolerate the TDM-guided dose increase(s) [7]. However, the impact of sunitinib TDM on clinical outcome remains to be established.

The pharmacokinetics of sunitinib have been well characterised in several compartmental models [8, 9]. Exposure–response relationships have also been established for several clinical outcome measures, such as time to tumour progression (TTP) and overall survival [6]. This enables the use of these models in Monte Carlo simulations to investigate sunitinib TDM strategies. In lieu of actual clinical data, this would enable clinical trial simulations to provide a 'best guess' estimate of the potential clinical outcome improvement due to TDM in patients treated with sunitinib [10–12]. These simulations could also help design prospective trials that aim to investigate the impact of TDM on clinical outcomes. This application of clinical trial simulations is extensively used during clinical drug development and allows estimation of required study size and follow-up times [10, 12, 13]. This ensures that clinical trials are only performed if they can be considered feasible, avoiding the unethical practice of underpowered trials [14–16].

Here, we combined the results from three published papers on the pharmacokinetics, efficacy and dose-limiting toxicity of sunitinib into a single simulation model [6, 7, 9]. Based on initial simulations, we decided to focus on the clinically relevant endpoint of TTP in patients with GIST. The Weibull model characterising the exposure–response relationship was estimated with low parameter uncertainty and described the published TTP data well [6]. However, this model does not allow for the incorporation of a change in exposure during the treatment period. This is a necessary feature to be able to characterise the effect of TDM-guided dose adaptations with the model. We therefore developed two alternative models by modifying the original Weibull model.

We used both of these models to estimate the clinical benefit of TDM of sunitinib in eligible patients with GIST. Additionally, we used clinical trial simulations to evaluate the design of a prospective trial that would be sufficiently powered to show an improvement in TTP when using TDM with sunitinib. Finally, we discuss the feasibility of such a trial and the implications of our findings for the efforts to individualise sunitinib dosing in patients with GIST.

Methods

Input–output model

A semi-physiological model by Yu et al. [9] was used to simulate sunitinib pharmacokinetics and its active metabolite SU12662. This model was developed using a pooled dataset of three clinical studies with a total of 70 patients with renal cell carcinoma, GIST or pancreatic neuroendocrine tumours. Patients received daily sunitinib doses of 25, 37.5 or 50 mg. The model's parameters are allometrically scaled with the patient's body weight. Body weight was simulated as in the original population PK model paper: as a log-normal distribution with a mean of 82.3 kg, standard deviation of 19.4 and truncated between 39 and 157 kg [9].

The effect of sunitinib exposure (steady-state daily AUC, in $\mu g\ h\ ml^{-1}$) on time to tumour progression in patients with GIST was simulated using the previously published Weibull distribution model [6]. If the virtual patient received no TDM-guided dose increase, the hazard rate function or tumour progression event rate $h(t, AUC)$, and the survival function $S(t, AUC)$ are described by the following equations [17]:

$$h(t, \mathrm{AUC}) = \ln\ 2 \times \frac{1.29}{t} \times \left(\frac{t}{57.1 + 213 \times \mathrm{AUC}}\right)^{1.29} \quad (1)$$

$$S(t, \mathrm{AUC}) = \exp\left(-\ln 2 \times \left[\frac{t}{57.1 + 213 \times \mathrm{AUC}}\right]^{1.29}\right) \quad (2)$$

where t is the time after initiation of sunitinib treatment in days. The above equations require a single value of steady-state sunitinib exposure; they do not allow the incorporation of a change in steady-state exposure during the treatment period. There are no available data to inform how the effect of a change in steady-state exposure (due to altered dose) could best be implemented in the survival and hazard functions. Because of this uncertainty, we developed two different sets of equations under different (optimistic versus conservative) assumptions.

In the first modified model, it is assumed that the original hazard rate function switches immediately from the pre-TDM to the post-TDM exposure on a certain time point after the TDM intervention (T_{switch}). We have set T_{switch} at Day 50, as the sunitinib exposure will have reached steady state even if patients received a dose increase on Day 42. This hazard function $h_{\mathrm{immediate}}(t)$ is described by Eq. 3. From that, the survival function $S_{\mathrm{immediate}}(t)$ is derived that is defined by Eq. 4 [17].

$$h_{\mathrm{immediate}}(t) = \begin{cases} h(t, \mathrm{AUC}_{\text{pre-TDM}}) & \text{if } t \le T_{\mathrm{switch}} \\ h(t, \mathrm{AUC}_{\text{post-TDM}}) & \text{otherwise} \end{cases} \quad (3)$$

$$S_{\mathrm{immediate}}(t) = \exp\left(-\int_0^t h_{\mathrm{immediate}}(t)\mathrm{d}t\right) \quad (4)$$

Here, $\mathrm{AUC}_{\text{pre-TDM}}$ is the steady-state exposure on the starting dose and $\mathrm{AUC}_{\text{post-TDM}}$ is the steady-state exposure

on the final, post-TDM dose. With this model, the hazard rate after T_{switch} only depends on the post-TDM exposure.

A second—more conservative—modified model was also developed, where the hazard rate at time t is calculated using the weighted exposure at time t. This method results in a more gradual effect of the change in exposure on the hazard rate than the immediate change of the first method. Before T_{switch}, the weighted exposure is equal to the pre-TDM steady-state exposure. After T_{switch}, the exposure is weighted depending on the time that has passed since T_{switch}, according to Eq. 5.

$$\mathrm{AUC}_w(t) = \begin{cases} \mathrm{AUC}_{\text{pre-TDM}} & \text{if } t \le T_{switch} \\ \frac{1}{t} \times \left(\mathrm{AUC}_{\text{pre-TDM}} * T_{switch} \right. & \\ \left. + \mathrm{AUC}_{\text{post-TDM}} * (t - T_{switch})\right) & \text{otherwise} \end{cases} \tag{5}$$

This weighted exposure $\mathrm{AUC}_w(t)$ is then used in the hazard function $h_{gradual}(t)$, which is defined in Eq. 6. The survival function can be derived from that, as shown in Eq. 7 [17].

$$h_{gradual}(t) = \ln 2 \times \frac{1.29}{t} \times \left(\frac{t}{57.1 + 213 \times AUC_w(t)}\right)^{1.29} \tag{6}$$

$$S_{gradual}(t) = \exp\left(-\int_0^t h_{gradual}(t)\mathrm{d}t\right) \tag{7}$$

With this modified model, the hazard rate after T_{switch} not only depends on the post-TDM exposure, but also on the pre-TDM exposure. The influence of pre-TDM exposure on the prognosis does diminish at higher values of t; at high values of t, $\mathrm{AUC}_w(t)$ will approach $\mathrm{AUC}_{\text{post-TDM}}$.

Trial execution model

The protocol of the simulated trial was based on a published sunitinib TDM trial by Lankheet et al. [7]. Virtual patients received a starting dose of 37.5 mg sunitinib daily. Dose adaptations were guided by measured TTL of sunitinib and SU12662. TTL was measured twice in each patient (day 14 and 35). Residual or unexplained variability identified in the original PK model was included in this measurement, 24.5 and 17.3 % variability for sunitinib and SU12662, respectively [9]. If a virtual patient had a measured TTL below the pharmacokinetic target of 50 ng ml^{-1}, then their dose was increased by 12.5 mg on day 21 (first TDM cycle) or on day 42 (second TDM cycle). The maximum daily dose was 62.5 mg, for those patients where both sequential TDM measurements were below the target TTL.

In simulations where dose-limiting toxicity (DLT) was implemented, patients with DLT were not eligible for dose increases even if they had TTL < 50 ng ml^{-1}. The prevalence of DLT in patients with TTL < 50 ng ml^{-1} was set at 67 %, comparable with that found in the sunitinib TDM feasibility study [7].

Study dropout (and the resulting censoring of time-to-event data) was implemented as two-week dropout rate of 0.2 %, which corresponds to a two-year dropout rate of approximately 10 %. This is equal to the dropout rate used in a previous clinical trial simulation of sunitinib [18].

Simulation

The different models were combined in R (version 3.2.2) and used in 10,000-patient Monte Carlo simulations. The simulated individual PK profiles and the (modified) Weibull models were used to generate individual survival functions. For each virtual patient, a single random sample from the individual's survival function was taken to yield the TTP. Data were considered censored if the planned follow-up time was shorter than an individual's TTP. Censoring was also applied upon study dropout before tumour progression. The R code used in the simulation can be found in the supplemental material.

Power estimation

The statistical power of trial designs was estimated by simulating 5,000 trials. All subjects start on a fixed-dose design of 37.5 mg once daily. Subjects with TTL < 50 ng ml^{-1} at Day 14 and no DLT were randomly allocated (1:1) to either fixed or TDM-guided dosing; other subjects were excluded from further analysis. The log-rank test (significance level = 0.05) was used to compare the Kaplan–Meier curves of TTP of both treatment groups. The statistical power was calculated by dividing the number of 'significant' trials by the total number of simulated trials [13]. By calculating the statistical power over a range of study sizes, the required study size to achieve 80 % power was estimated.

This procedure was repeated for studies with different follow-up times and model assumptions (dropout rate, occurrence of dose-limiting toxicity and hazard function used). The following values of the biweekly dropout rate were investigated: 0.1, 0.2 (base scenario), 0.6 and 1.0 %. Study follow-up times of 1.0, 1.5, 2.0 (base scenario) and 3.0 years were investigated. The occurrence of DLT was included at 42, 67 (base scenario) and 85 %. These numbers are based on the proportion of DLT in patients with TTL < 50 ng ml^{-1} of the published sunitinib TDM trial and the corresponding confidence interval of that proportion [7].

Results

The simulated PK profiles of eligible (i.e. without DLT) patients with and without TDM are shown in Fig. 1. Before TDM, 52 % of the patients have TTL below the target of 50 ng ml^{-1}. This number is reduced to 30 and 16 % after one or two rounds of TDM, respectively. TDM increases the median TTL from 49.2 to 62.2 ng ml^{-1}. Because residual variability was included in the TDM measurements, not all virtual patients with a 'true' TTL < 50 ng ml^{-1} received a dose increase: the sensitivity is 88 and 81 % for the first and second cycle, respectively. Likewise, some virtual patients with TTL ≥ 50 ng ml^{-1} received a dose increase during the two TDM cycles (16 and 15 %, respectively). The majority of the virtual patients (63 %) received at least one dose increase, with 27 % receiving a dose increase in both TDM cycles. Of the patients who failed to reach target TTL at the end of the simulation, 65 % received the 12.5 mg dose increase during both TDM rounds (i.e. final dose of 62.5 mg daily). Two rounds of TDM reduced the interindividual variability in measured TTL from 43 to 32 %.

To be able to incorporate the change of exposure from TDM-guided dose adaptations, we developed two modified models from the original Weibull model. These models assume either an 'immediate' or a 'gradual' effect of the change of exposure (after T_{switch} or day 50) on the hazard rate of tumour progression. Both models are equivalent to the original Weibull model when there is no change in steady-state exposure (due to a constant dose).

The behaviour of these modified models is further illustrated in Fig. 2. Before T_{switch}, the survival curve is only determined by the pre-TDM exposure. This can be seen in the graph from the initial overlap of the fixed AUC low curve and the two modified models with TDM. After T_{switch}, the modified models change from a low to high exposure, resulting in a lower hazard rate. This effect is more pronounced in the 'immediate' effect model, although both models show a clear improvement over the survival curve of a fixed low AUC.

These two models were then used to simulate the individual TTP from the individual sunitinib exposure of the virtual patients (Fig. 3). For patients with TTL < 50 ng ml^{-1}, the median TTP was 216 days when a fixed-dosing strategy was applied. Patients with TTL ≥ 50 ng ml^{-1} had a better prognosis, with a median TTP of 323 days. When the impact of a TDM intervention was simulated, the median TTP of patients with an initial TTL < 50 ng ml^{-1} increased to 249 days (+15 %) and 283 days (+31 %) for the 'gradual' and 'immediate' effect simulation, respectively.

We then simulated a series of randomised prospective clinical trials that compared TDM-guided with fixed dosing. These simulations included clinical issues such as DLT and dropout rate. Under the 'immediate' effect model, these simulations predicted that 1600 patients would need to be enroled in such a trial to be sufficiently powered to show a significant improvement in TTP (as defined above) due to the TDM intervention. However, if the impact of TDM would be 'gradual', the required study size would be 3900. This is consistent with the more conservative impact of TDM on clinical outcome with the 'gradual' effect model.

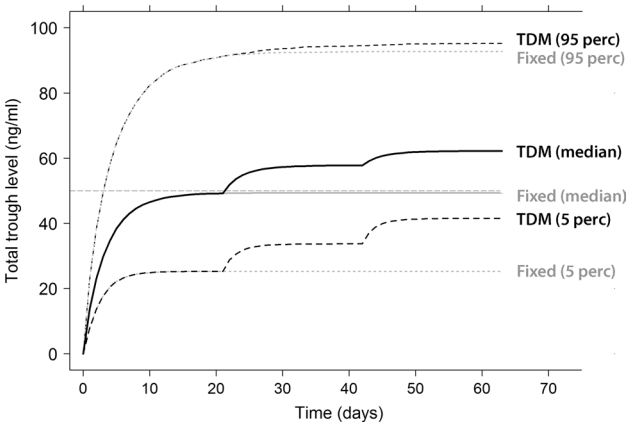

Fig. 1 Effect of sunitinib therapeutic drug monitoring (TDM) on total trough level (TTL). Shown is the median predicted TTL and the 90 % prediction interval. For the TDM cohort, dose increases are given on day 21 and 42 to patients with a measured TTL below 50 ng ml^{-1} on day 14 and 35, respectively. *Perc* percentile

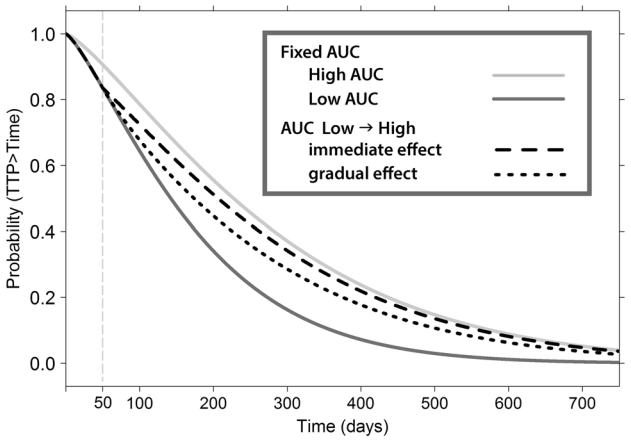

Fig. 2 Behaviour of (modified) Weibull function of exposure (AUC)–response relationship of sunitinib on time to tumour progression (TTP). The *solid grey line* represents the original Weibull function with single value of exposure (low or high). The *broken lines* represent the modified Weibull functions with two values of exposure; low until T_{switch} (day 50) and high thereafter. Low = 0.4 μg h ml^{-1}, high = 0.8 μg h ml^{-1}

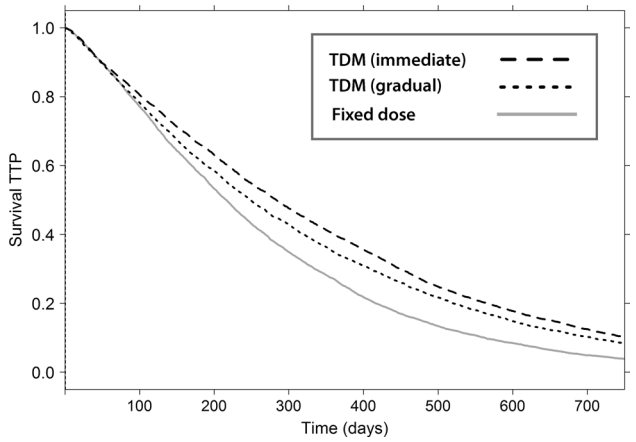

Fig. 3 Simulated time to tumour progression for fixed versus therapeutic drug monitoring (TDM)-guided dosing. *TTP* time to tumour progression

In the above clinical trial simulations, we used a base scenario of a trial with a follow-up of two years, a biweekly dropout rate of 0.2 % and a prevalence of DLT of 67 % of the patients with TTL < 50 ng ml^{-1}. We repeated the power estimation for different values of these parameters, to investigate their impact on the required study size (Fig. 4). Increasing the follow-up time from 2 to 3 years resulted in only a modest reduction in required study size (1500 instead of 1600 subjects). The assumed dropout rate also has only a modest effect on the required study size. Increasing the biweekly dropout rate to 1 % (a fivefold increase from the base scenario) resulted in only a 26 % increase in required study size. The prevalence of DLT, however, has a strong effect on the required study size (Fig. 4).

Discussion

In this study, we used Monte Carlo simulations to study the potential impact of sunitinib TDM on the pharmacokinetics and clinical outcomes of patients with GIST. Our main finding is that sunitinib TDM might increase the median time to tumour progression by about 1–2 months (15–31 %) in eligible patients with GIST.

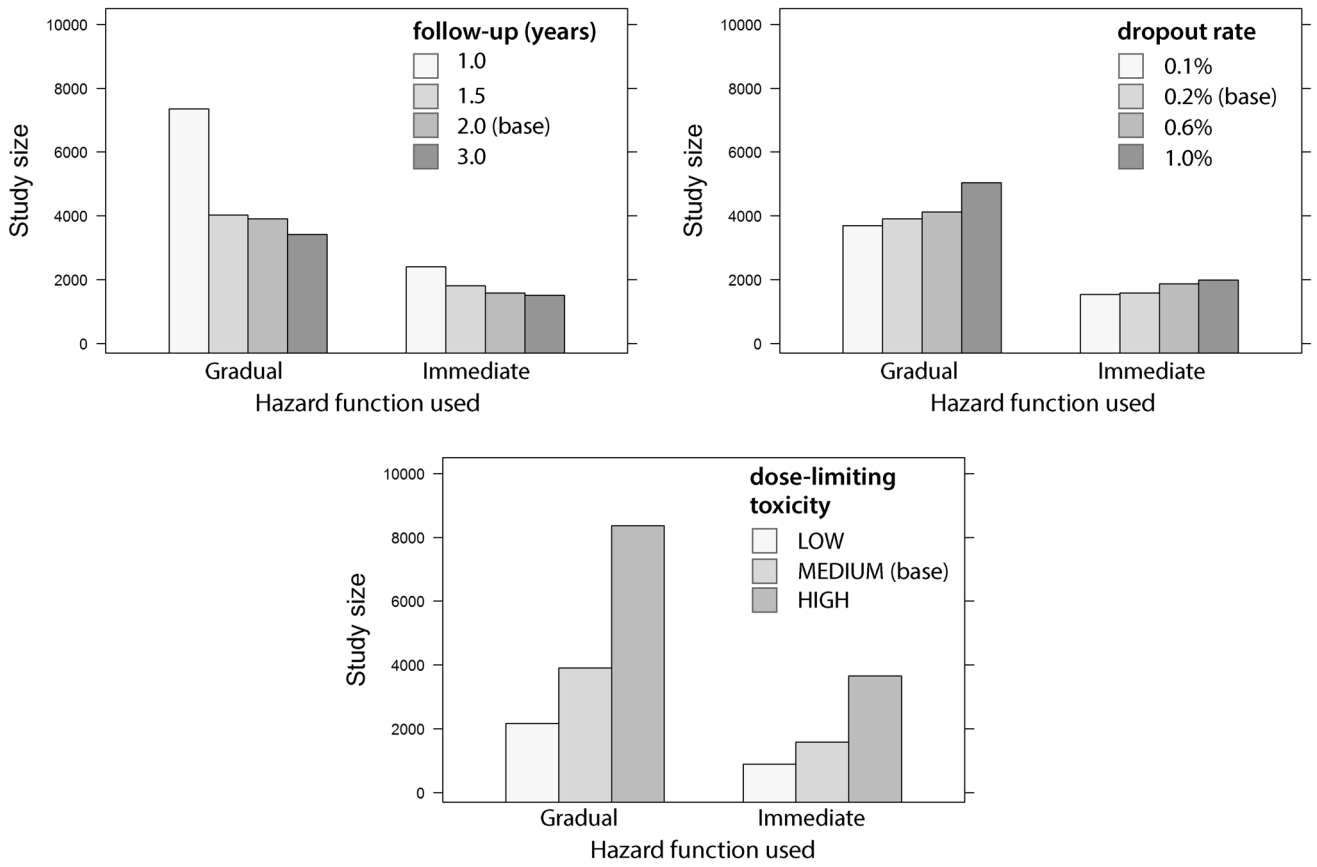

Fig. 4 Required TDM study size for different study designs and model assumptions. Dropout rate is defined as the biweekly chance of dropping out. Prevalence of dose-limiting toxicity in patients with total trough levels below 50 ng ml^{-1}: low (42 %), medium (67 %), high (85 %)

The original Weibull model for TTP from Houk et al. [6] could be modified to allow the implementation of changing drug exposure after TDM-guided dosing. Because of the lack of clinical data, it is unknown how changes in drug exposure will affect the TTP hazard rate. In consideration of this uncertainty, we performed all our simulations with two different types of modified Weibull models: one with an 'immediate' effect of the exposure change and another (more conservative) model with a more 'gradual' effect. Both of these models showed a clinically relevant increase in TTP in eligible patients, although the effect was more pronounced in the immediate effect model.

There are other ways in which we could have modified the original Weibull model, in addition to our 'immediate' and 'gradual' effect model. For instance, one could use a model under the assumption that the hazard function relies on the average AUC of the last 28 days. This kind of model would be more gradual than the 'immediate' model, but also faster than our 'gradual' effect model. Due to lack of data, we cannot establish which of these (and many other possible) Weibull models would be most appropriate to model the effect of exposure change on TTP. Instead, we decided to use two models that represent two extremes of the spectrum: an optimistic 'immediate' effect model where the hazard rate only depends on the current exposure and a more conservative 'gradual' effect model where the hazard rate depends on the exposure during the entire treatment period until that point. It seems plausible that the expected clinical outcome improvement would be in the range predicted by these models, although we cannot rule out the possibility that the clinical outcome improvement will be lower than that predicted by the 'gradual effect' model.

Because of this uncertainty, it would be preferable to validate our findings in a randomised clinical trial where a fixed dosing and TDM-guided dosing are compared. With our simulation models, we were able to obtain estimates of the required number of patients that would be needed to perform such a trial with sufficient statistical power. Even when assuming an immediate effect of the changing exposure on the TTP hazard rate, an estimated 1600 subjects would need to be included. This study size is about fivefold larger than that of the pivotal phase III trial that supported market authorisation of sunitinib for GIST [19]. Because GIST is a relatively rare form of cancer and sunitinib is not the first-line treatment option, the recruitment of 1600 patients for a TDM trial would be virtually impossible. However, performing a trial with a lower number of patients should be considered unethical due to insufficient statistical power [15, 16].

By repeating our power simulations with different assumptions and follow-up time, we were able to evaluate their influence on the required study size (Fig. 4). This revealed that increasing the follow-up time from 2 to 3 years results in a marginal reduction in required study size, probably because at 2 years the study is already at >90 % maturity. The prevalence of dose-limiting toxicity on the other hand has a very strong effect on the required study size. This is to be expected, as only patients without dose-limiting toxicity were eligible for being randomised to the TDM-guided dose increases. For example, in the scenario with high DLT (85 %), only 15 % of the patients with TTL < 50 ng ml^{-1} would be eligible for randomisation.

Our analysis depended on the availability of a published exposure–response relationship for sunitinib. For many other kinase inhibitors under investigation for TDM, the exposure–response relationship is still unknown [2]. In other cases, it is poorly defined and only analysed with ROC (received operating characteristics) curve, which gives a cutoff point between high and low exposure. Although this cutoff point can be a convenient point of reference for clinical practice, it cannot be used for realistic simulations of clinical outcome. There is thus a need for further publication of suitable (continuous) exposure–response relationships of kinase inhibitors. In addition to increasing our understanding of the pharmacology of these agents, such models allow us to perform simulation exercises similar to those presented here [11].

Although we used sunitinib AUC to predict patient TTP, the simulated dosing decisions were based on measured TTL. This was done because for TTL, a therapeutic window has been published (50–100 ng ml^{-1}) [2]. More importantly, the TTL can be obtained from a single-plasma sample, making it more convenient for TDM in a clinical setting than a TDM service based on sunitinib AUC.

In this study, we investigated the impact of TDM only on TTP. Although a Weibull model of the exposure–overall survival relationship was also reported in the same paper, initial simulations with this model did not match real data as well as the TTP Weibull model; overall survival for patients with low exposure was overestimated, while that of patients with high exposure was underestimated (data not shown). We can therefore not exclude the possibility that a TDM trial with overall survival as its primary outcome would have a significantly smaller (or larger) required study size than a trial focusing on TTP. The objective response rate was not a suitable alternative outcome measure, as there appears to be no exposure–response relationship for this outcome in patients with GIST [6].

The fixed-dosing strategy in our simulations was 37.5 mg once daily continuously. This matches the starting dose of the only sunitinib TDM trial published so far [7]. This allowed us to get an indication of the prevalence of dose-limiting toxicity in patients with TTL < 50 ng ml^{-1}. Other fixed-dosing strategies were not included in this simulation study, such as 50 mg once daily in 6-week cycles (four on, two off). Although this is the recommended

starting dose regimen for sunitinib, a recent post-marketing study revealed that almost half of the patients on sunitinib for GIST receive a different regimen [20]. Several trials have suggested that continuous dosing has comparable efficacy in GIST [5, 21, 22].

While the randomised clinical trial is considered the gold standard of evidence for clinical practice, our results suggest that this would not be an option for investigating the clinical impact of sunitinib TDM in patients with GIST. However, our simulations also suggest that for patients that are eligible for TDM-guided dose increases, significant improvement in TTP can be achieved. Considering the current lack of data and low number of patients, modelling and simulation might be the key to evaluating TDM strategies in GIST and other rare types of cancers. The FDA suggests that exposure–response models might be used to develop ways to individualise treatment in patient subsets for which there are limited data [11]. Simulations have been used to evaluate the benefit of TDM of several antibiotics and immunosuppressants [23–25]. Booth et al. [26] used simulations to investigate different paediatric dosing strategies for busulfan and to identify a need for TDM.

Considering the combined evidence from this study and previous published work on sunitinib, we would argue that there is enough evidence to consider implementation of sunitinib TDM in the treatment of GIST. For rare cancers with well-defined exposure–response relationships, modelling and simulation might allow the optimisation of dosing strategies when clinical trials cannot be performed due to low number of patients.

Compliance with ethical standards

Conflict of interest None.

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