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ORIGINAL ARTICLE

Dose adaptation of capecitabine based on individual prediction of limiting toxicity grade: evaluation by clinical trial simulation

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Abstract
Purpose Anticancer drugs often show a narrow therapeutic index and high inter-patient variability, which can lead to the need to adjust doses individually during the treatment. One approach to doing this is to use individual model predictions. Such methods have been proposed to target-specific drug concentrations or blood cell count, both of which are continuous variables. However, many toxic effects are evaluated on a categorical scale. This article presents a novel approach to dose adjustments for reducing a graded toxicity while maintaining efficacy, applied to hand-and-foot syndrome (HFS) induced by capecitabine.
Methods A mixed-effects proportional odds Markov model relating capecitabine doses to HFS grades was individually adjusted at the end of each treatment cycle (3 weeks) by estimating subject-specific parameters by Bayesian MAP technique. It was then used to predict the risk of intolerable (grade ≥ 2) toxicity over the next treatment cycle and determine the next dose accordingly, targeting a predefined tolerable risk. Proof of concept was given by simulating virtual clinical trials, where the standard dose reductions and the prediction-based adaptations were compared, and where the therapeutic effect was simulated using a colorectal tumor inhibition model. A sensitivity analysis was carried out to test various specifications of prediction-based adaptation.
Results Individualized dose adaptation might reduce the average duration of intolerable HFS by 10 days as compared to the standard reductions (3.8 weeks vs. 5.2 weeks; 27% relative reduction) without compromising antitumor efficacy (both responder rates were 49%). A clinical trial comparing the two methods should include 350 patients per arm to achieve at least 90% power to show a difference in grade ≥ 2 HFS duration at an alpha level of 0.05.
Conclusions These results indicate that individual prediction-based dose adaptation based on ordinal data may be feasible and beneficial.

Keywords Capecitabine · Hand-and-foot syndrome · Dose adaptation · Cancer chemotherapeutics · Computer modeling and simulation · Pharmacometrics

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Introduction

The management of anticancer therapies is complicated by their narrow therapeutic indices (range between the minimum effective and toxic doses) and high inter- and intra-patient variability in pharmacokinetics (PK) and pharmacodynamics (PD). Dose scaling to body surface

area is used for most anticancer drugs, although this approach reduces some of the PK-variability for only a few drugs [1]. The overall objective for optimizing a dosing regimen is that each patient obtains the maximum possible anticancer effect without being subjected to an unacceptable risk of severe toxicities. To achieve this therapeutic goal, strategies for dose adaptation before and/or during the treatment are required. Because the dose reductions commonly applied after the occurrence of severe toxicity are suspected to be less than optimal, individualized dose adjustment alternatives are of high clinical relevance. The population model-based dose adaptation approach was first introduced by Sheiner [2]. The main idea is to individualize a population model relating dosage to a pharmacokinetic or pharmacodynamic outcome by Bayesian techniques, using data from the patient's previous responses to the drug. The optimal dosage is then determined based on individual response predictions given by the patient-specific model.

Bayesian dose adaptations are used widely to control the plasma concentrations of various classes of drugs or their active metabolites; a few examples have been developed for anticancer drugs too [3–5]. This is reasonable only if plasma concentration correlates strongly with the toxic outcomes, which is seldom the case for anticancer drugs [3]. In the absence of such direct relationships, PK-based control is not adequate. The alternative is to investigate the feasibility of dose adaptation based on toxicity predictions, without compromising the efficacy. Moreover, because toxicity is often measured on an ordinal and not a continuous scale, the usual model-based adaptive control techniques are not directly applicable and ordinal data-specific criteria must be determined.

Capecitabine (Xeloda, Roche) is an oral prodrug of 5-fluorouracil (5FU), a chemotherapeutic agent commonly used to treat solid tumors [6]. Because it is preferentially metabolized to the active molecule 5FU in tumor tissues, capecitabine is less toxic to healthy tissues [7], while having non-inferior efficacy as compared to intravenously administered 5FU (commonly given in conjunction with leucovorin (5FU/LV)) [8, 9]. However, hand-and-foot syndrome (HFS) is experienced by much more patients treated with capecitabine (60%) than with 5FU/LV (15%). This syndrome manifests as redness, swelling, numbness, or even painful blisters and desquamation of palm and sole skin, and often disturbs the daily activities of patients. HFS is measured on an ordinal scale of severity from grade 0 (none) to grade 3 (severe). According to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 [10], grade 1 HFS is characterized by skin changes without pain, grade 2 by skin changes with pain not interfering with function, and grade 3 by skin changes with pain interfering with function. Grade 1 toxicity is considered acceptable within the context of cancer treatment and does not require any dosage modification. According to manufacturer's prescription guidelines [11], the occurrence of grade 2 or higher toxicity is considered intolerable and indicates treatment interruption until remission or at least decrease to grade 1 severity. Treatment is then reinitiated at a reduced dose (reduced by 25 or 50%) depending on the number of previous toxicity events. After the third event with grade 3 or the fourth with grade 2, treatment with capecitabine is terminated. However, the standard crude dose reductions may not be optimal and the therapeutic benefit might be improved by making patient-specific dose adaptations using model-based predictions. In addition, as with many anticancer drugs, no direct relationship between occurrence of HFS and plasma concentration of capecitabine or its metabolites has been detected. Pathophysiology of HFS has not been understood yet, and HFS is only suspected to be induced by the accumulation of the drug in the skin [12]. Therefore, the dosage of capecitabine should be based directly on the risk of intolerable grade HFS while maintaining at least the same efficacy in terms of tumor growth inhibition.

The present work aimed at developing an algorithm for individual prediction-based dose adaptation (IPBDA) based on a mixed-effects model for categorical endpoints. It is a direct application of the capecitabine-induced hand-and-foot syndrome model [13]. The method had to respect the requirement not to reduce the antitumor efficacy of the treatment, which was simulated using a colorectal tumor inhibition model [14]. The proof of concept was given by performing computer simulations of clinical trials that compared the standard and IPBDA methods.

Methods

Population hand-and-foot syndrome model

A mixed-effects proportional odds Markov model for an adverse effect called hand-and-foot syndrome (HFS) caused by the anticancer drug capecitabine has been described in [13], and we give only details relevant to the present simulation study.

While capecitabine is taken twice a day at 1,250 mg/m^2, this model assumes a total daily dose of 2,500 mg/m^2 is administered once a day. Because capecitabine is available in tablets of 150 and 500 mg and is taken twice per day, the manufacturer recommends to round the doses to 3,000; 3,300; 3,600; 4,000; 4,300; …; 5,600 mg per day, so that equal amounts can be taken in the morning and in the evening [11]. The drug was administered on a 3 weeks cycle basis: 2 weeks of treatment followed by 1 week of rest.

The severity of HFS is evaluated by grades from 0 (none) to 3 (severe). Since the frequency of grade 3 was low, grades 2 and 3 were combined into a single category

of grade ≥2 in the original model. HFS grade was evaluated once each week. The probabilities of grades are considered dependent on the preceding grade, i.e., a first-order Markov effect was incorporated in the population model. The model predicts that the overall distribution of grades in the treated population over 30 weeks (when standard dose adaptation is used) is approximately 66, 18 and 16% for grade 0, 1 and ≥2, respectively.

Due to the absence of pharmacokinetic data, the drug effect was quantified by a kinetic-pharmacodynamic (KPD) model [15], which relates the pharmacodynamic response to the administered drug doses without specifying a pharmacokinetic model. It is analogous to a PKPD model but the letter P is omitted to emphasize that PK is not measured. The principal idea of a KPD model is to assume a virtual compartment representing the biophase in which the concentration is in equilibrium with the observed effect. The elimination rate constant, K, from the virtual compartment governs the delay between the rate of dose administration and the observed effect. The parameter ED_{50} is the apparent in vivo potency of the drug at steady state, equal to the product of EC_{50}, the pharmacodynamic potency, and clearance, the PK "potency" at steady state.

The drug effect on the log-odds (logit) of the cumulative probabilities of grades is specified by an E_{MAX} function. The renal function (measured by creatinine clearance (CLcr) calculated using the Cockcroft–Gault formula [16]) at baseline was found to explain some of the interindividual variability and was included as an additive linear effect on the intercept [13], which corresponds to the idea that the better the renal function, the lower the patient's risk is. The full model is given below:

$$\frac{dQ(t)}{dt} = \text{Dose}(t) - K \cdot e^{\eta_{1i}} \cdot Q(t),$$

where $Q(t)$ is the accumulated drug amount in the virtual compartment at time t, Dose(t) is the amount of capecitabine administered at time t, 0 otherwise.

$$\text{logit}[P(Y_{it} \le 0 | Y_{it-1} = G^*)] = B_0^{G^*} - \frac{E_{\text{MAX}}^{G^*} \cdot (Q_{it} \cdot K \cdot e^{\eta_{1i}})}{ED_{50} + (Q_{it} \cdot K \cdot e^{\eta_{1i}})} + (\text{CLcr}_i - 75.5) \cdot \theta_{\text{CLcr}} + \eta_{2i}$$

$$\text{logit}[P(Y_{it} \le 1 | Y_{it-1} = G^*)] = B_0^{G^*} + B_1^{G^*} - \frac{E_{\text{MAX}}^{G^*} \cdot (Q_{it} \cdot K \cdot e^{\eta_{1i}})}{ED_{50} + (Q_{it} \cdot K \cdot e^{\eta_{1i}})} + (\text{CLcr}_i - 75.5) \cdot \theta_{\text{CLcr}} + \eta_{2i}$$

where Y_{it} is ith patient's grade at week t, G^* is the preceding grade (at week t–1); the baseline logit parameters, $B_0^{G^*}$ and $B_1^{G^*}$, as well as the maximum effect parameter, $E_{\text{MAX}}^{G^*}$, depend on G^* (i.e., each has three different values for $G^* = 0,\ 1,\ \ge 2$); η_{1i} and η_{2i} are individual-specific random effects, corresponding to the elimination rate constant K and the intercept, respectively. η_{1i} and η_{2i} follow a bivariate normal distribution with mean 0 and variance–covariance matrix Ω. η_{1i} adjusts the K value as an exponential multiplier ($K_i = K \cdot e^{\eta_{1i}}$,) while η_{2i} has an additive effect on the intercept.

The grade probabilities are obtained by the following transformations:

$$p_{it0} = P(Y_{it} = 0 | Y_{it-1} = G^*) = P(Y_{it} \le 0 | Y_{it-1} = G^*)$$
$$p_{it1} = P(Y_{it} = 1 | Y_{it-1} = G^*) = P(Y_{it} \le 1 | Y_{it-1} = G^*) - P(Y_{it} \le 0 | Y_{it-1} = G^*)$$
$$p_{it2} = P(Y_{it} = 2 | Y_{it-1} = G^*) = 1 - P(Y_{it} \le 1 | Y_{it-1} = G^*)$$

The model parameter estimates (as published in [13]) are given in Table 1.

Dose adaptation procedures

Standard dose adaptation was to reduce the initial dose by 25% after the second event with HFS grade >2 and by 50% after the third event.

Individual prediction-based dose adaptation (IPBDA) procedure consisted of: (1) estimating the individual random effects using both the data of the patient's past observations of HFS and the population model (the estimation step); (2) choosing the new dose so that the average risk of HFS grade ≥2 over the next 3 weeks would be closest to (but not greater than) the target risk (the dose calculation step).

The estimation step

Empirical Bayes' estimates (EBEs) of the individual random effects were obtained by the *maximum* a posteriori (MAP) method using the simplex optimization algorithm

Table 1 Hand-and-foot syndrome model parameter values [13]

Parameter	Value		
	$G^* = 0$	$G^* = 1$	$G^* = 2$
$B_0^{G^*}$	4.14	0.855	1.47
$B_1^{G^*}$	0.626	7.24	0.33
$E_{\text{MAX}}^{G^*}$	3.17	6.65	8.92
K		0.102	
ED_{50}		12,900	
θ_{CLcr}		0.0065	
ω_{η_1}		0.954	
ω_{η_2}		1.5	
$\text{corr}(\eta_1, \eta_2)$		0.67	

G^* HFS grade at previous week, ω_η standard deviations of random effects

Parameter significations are given in the text

[17]. Population parameters were not reestimated but fixed to their true value.

The distribution of $\eta_i = \begin{pmatrix} \eta_{1i} \\ \eta_{2i} \end{pmatrix}$ was assumed to be bivariate normal N(0, Ω), where

$$\Omega = \begin{bmatrix} \omega^2_{\eta_1} & \rho\omega_{\eta_1}\omega_{\eta_2} \\ \rho\omega_{\eta_1}\omega_{\eta_2} & \omega^2_{\eta_2} \end{bmatrix},$$

$$\rho = \mathrm{corr}(\eta_1, \eta_2) = \frac{\mathrm{cov}(\eta_1, \eta_2)}{\omega_{\eta_1}\omega_{\eta_2}}.$$

The likelihood function for the HFS grade at week t was denoted $\rho(Y_{it}|D_{it}, Y_{it-1}, \Theta, \mathrm{CLcr}_i, \eta_i)$, where $D_{it} = (\mathrm{dose}_{i1}, \ldots, \mathrm{dose}_{it})$ is the ith patient's dosing history, and the total set of population parameters was $\Theta = (B^0_0, B^1_0, B^2_0, B^0_1, B^1_1, B^2_1, E^0_{\mathrm{MAX}}, E^1_{\mathrm{MAX}}, E^2_{\mathrm{MAX}}, ED_{50}, K, \theta_{\mathrm{CLcr}}, \omega_{\eta_1}, \omega_{\eta_2}, \rho)$.

The indicator variable, z_{itg}, was used to indicate the toxicity grade of the ith patient at week t:

$$z_{itg} = \begin{cases} 1, & \text{if } Y_{it} = G, \\ 0, & \text{otherwise.} \end{cases} \text{with} \quad G = \{0, 1, \geq 2\}.$$

The likelihood of a single observation for the ith patient at week t, conditional on the individual parameter values η_i, was given by $p(Y_{it}|D_{it}, Y_{it-1}, \Theta, \mathrm{CLcr}_i, \eta_i) = \prod_{g=0}^{2} p_{itg}^{z_{itg}}$, with p_{itg} as defined in the model description.

The likelihood of all observations of the ith patient till week t was given by:

$$\prod_{j=1}^{t} p(Y_{ij}|D_{ij}, Y_{ij-1}, \Theta, \mathrm{CLcr}_i, \eta_i) = \prod_{j=1}^{t}\prod_{g=0}^{2} p_{ijg}^{z_{ijg}}.$$

The a posteriori distribution of η_i was obtained by applying Bayes' rule:

$$p(\eta_i|H_{it}, D_{it}, \Theta, \mathrm{CLcr}_i) = \frac{p(\eta_i) \cdot \prod_{j=1}^{t} p(Y_{ij}|D_{ij}, Y_{ij-1}, \Theta, \mathrm{CLcr}_i, \eta_i)}{p(H_{it})},$$

where $H_{it} = (Y_{i1}, \ldots, Y_{it})$ is the toxicity history for the ith patient.

The estimates of ith patient's random effects at week t were given by the mode of their a posteriori distribution:

$$\hat{\eta}_{it\mathrm{MAP}} = \mathrm{Arg}\left[\max_{\eta_i} \frac{p(\eta_i) \cdot \prod_{j=1}^{t} p(Y_{ij}|D_{ij}, Y_{ij-1}, \Theta, \mathrm{CLcr}_i, \eta_i)}{p(H_{it})}\right].$$

The calculation was performed using the simplex optimization algorithm [17], coded in Fortran 77 adapted from [18].

The dose calculation step

After the first appearance of HFS (any grade >0), the most appropriate dose for the next treatment cycle was considered to be the one with which the average predicted probability of HFS grade ≥2 over the next cycle (3 weeks) was closest to (but not higher than) the "target" risk of 4% (determined by sensitivity analysis). The lower limit of reduction was 50% of the nominal dose. The upper limit depended on the patient's HFS and tumor response history: if the patient was still in stable disease, doses could be increased up to 150% of the nominal dose after the first 4 cycles if the patient had no HFS at all or if grade 1 lasted for at least 6 consecutive weeks. If grade ≥2 had been observed at any time previously, the upper dose limit was the nominal dose (100%). Before reduction, possible daily doses were from 3,000 to 5,600 mg, with increments of 300 or 400 mg (3,000; 3,300; 3,600; 4,000; 4,300; …), according to prescription guidelines [11]. For adapted doses, the lower limit was 1,600 mg (closest to 50% of the minimal initial dose of 3,000 mg), the upper limit was 5,600 mg (the highest dose recommended in the prescription guidelines [11]). Once started, dose adaptation was made before starting each new cycle, after reestimation of the patient's HFS model random effects.

Colorectal tumor model

The tumor growth inhibition model was developed using phase II data capecitabine ($n = 34$) and phase III data of fluorouracil ($n = 252$) in advanced and/or metastatic colorectal cancer [14]. In our simulation study, we used only the parameter values estimated on capecitabine data. It describes tumor size (the sum of the longest diameters of target lesions) as a function of time and drug exposure. It accounts for the dynamics of natural tumor growth (k_g) and for the antitumor drug effect (k_d), as well as development of resistance to it (λ). The model is described by the following differential equation:

$$\frac{dy(t)}{dt} = k_g \cdot y(t) - k_d(t) \cdot \mathrm{Exposure}(t) \cdot y(t),$$
$$y(0) = \mathrm{baseline},$$

with $k_d(t) = k_{d,0} \cdot e^{-\lambda \cdot t}$, in which $y(t)$ is the tumor size at week t, Exposure(t) is the daily dose at week t. Inter-patient variability in the model parameters (k_g, k_d and λ) was assumed to be lognormally distributed. The values of parameters are given in Table 2.

Disease status

Dynamics of the disease was classified similarly to response evaluation criteria in solid tumors (RECIST) 1.1. [19] to:

Table 2 Colorectal tumor inhibition model parameter values [14]

Parameter	Value	Interindividual variance	CV%
Tumor growth rate k_g (week^{-1})	0.021	0.499	80
Drug cell kill rate k_d (week^{-1})	0.025	0.388	69
Resistance appearance rate λ (week^{-1})	0.053	1.260	159

CV coefficient of interindividual variability

- complete response (CR): observed sum of longest diameters <10 mm;
- partial response (PR): observed >30% reduction from baseline;
- progressive disease (PD): >20% and at least 5 mm increase above lowest observed value;
- stable disease (SD): all other cases.

In silico clinical trial protocol

One treatment cycle corresponded to 2,500 mg/m^2/day for 2 weeks, followed by 1 week rest. Treatment was interrupted in case of grade ≥2 HFS, until recovery to grade ≤1. Subsequent doses were modified according to the corresponding protocol. Fifty thousand patients per arm were simulated. Trial duration was 30 weeks. Patients were assumed to drop out of the trial if grade ≥2 HFS lasted more than 6 weeks or reoccurred for the 4th time, also if disease progression was observed. If patients had a complete response, they ended the treatment after 6 treatment cycles had been completed. HFS was monitored for 4 weeks after the end of treatment.

Simulation of the clinical trial data

The HFS grades were generated at the end of each week by simulation from the HFS model. Creatinine clearance (CLcr) and body surface area (BSA) values were randomly drawn from distributions estimated from a representative dataset of 595 patients used for HFS model building: a normal distribution with mean = 1.82 and standard deviation (SD) = 0.227 for BSA, and a log-normal distribution for CLcr with mean of log(CLcr) = 4.34 and SD of log(CLcr) = 0.349. The ranges were limited to [1.19, 2.5] for BSA and to [26.9, 218.5] for CLcr, according to the extreme values observed in the mentioned dataset. Individual random effects were drawn from a bivariate normal distribution with parameter values given in Table 1. The toxicity grades were obtained by random sampling according to the probability model. Tumor size baseline (base) observations were generated by sampling from a lognormal distribution with mean(log(base)) = 4.25 and SD(log(base)) = 0.5, with minimum accepted values equal 10 mm. This distribution corresponded to baseline data from the dataset used to estimate the tumor model. Subsequent observations were generated every 6 weeks by integrating the differential equation and then "adding" the measurement error: observation = true value * exp(error), with error sampled from a normal distribution with mean = 0 and SD = 0.25. Individual random effects were drawn from normal distributions with parameter values given in Table 2. The simulation of the trial was coded and performed in Fortran.

Criteria for comparing dose adaptation methods

Dose adaptation methods were compared in terms of toxicity related criteria: % of patients having (one and reoccurring) events with grade ≥2 HFS, average number of weeks with grade ≥2 HFS, average duration of reoccurring events with grade ≥2 HFS, % of patients who dropout due to HFS; as well as efficacy related criteria: % of patients having tumor response (PR + CR), % of patients who have progression of disease, relative change from baseline of tumor sizes.

Power analysis

In order to investigate the statistical power of the clinical trial for demonstrating the superiority of individualized dose adaptation versus the standard method, 100 replicate trials with 300, 350 and 600 patients per arm were simulated. The Wilcoxon rank sum test was used to test the difference in the total duration of time spent in HFS grade ≥2. The proportion of simulated studies with $P \leq 0.05$ gave the power for detecting a significant difference at $\alpha = 0.05$.

Results

Table 3 summarizes the main results of the virtual clinical trial, which compared the standard dose adaptation (reductions by 25 or 50%) and the individual prediction-based one, which uses the patient's HFS model to predict the future risk of grade ≥2 HFS and determines the next cycle dose accordingly. The overall dynamics of the

Table 3 Results of the two dose adaptation methods

Criteria	Standard	IPBDA
Toxicity (HFS)		
Average number of weeks with grade ≥2	5.2	3.8
Percentages of patients having grade ≥2	55.5	55.2
Percentages of patients having reoccurring events with grade ≥2	13.6	12.6
Duration of reoccurring events with grade ≥2 (weeks)	5.7	5.0
Percentages of patients who dropout due to HFS	23.2	21.6
Therapeutic efficacy		
Percentages of responders (CP + PR)	49.2	49.4
Percentages of patients who have disease progression	31.7	31.9
Relative change from baseline (median), %	−23.3	−23.1

IPBDA individual prediction-based dosage adaptation, *HFS* hand-and-foot syndrome, *CR* complete response, *PR* partial response

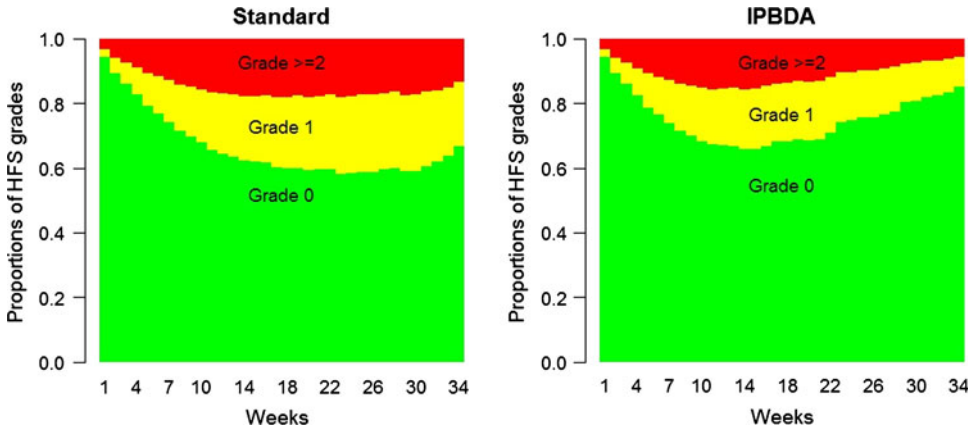

Fig. 1 Dynamics of the distributions of hand-and-foot syndrome grades with the standard dose adaptation (*left panel*) and the individual prediction-based one (IPBDA) (*right panel*)

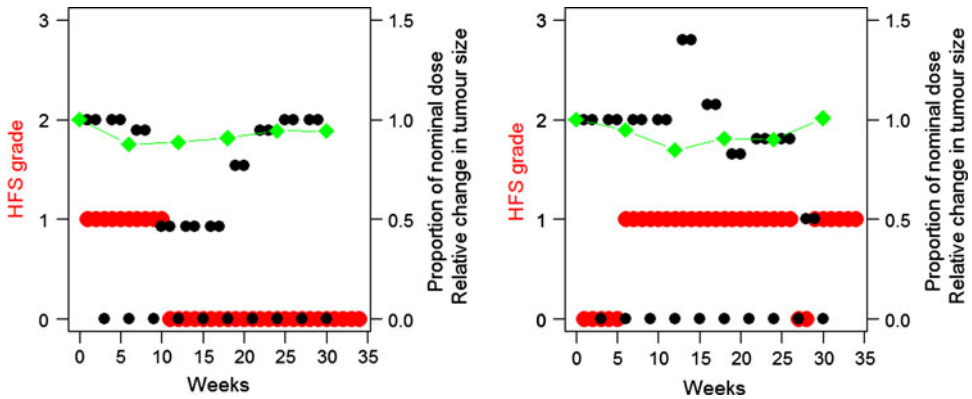

Fig. 2 Examples of individual changes in doses, HFS grades and tumor sizes. *Black dots* correspond to the dose amount relative to the initial dose; *red dots* correspond to the HFS grades; *green linked diamonds* correspond to tumor sizes relative to the initial size

distributions of grades in the two adaptation arms are shown in Fig. 1; a couple of examples of individual changes in the dose and HFS grade are shown in Fig. 2. The average total duration of grade ≥2 HFS was approximately 10 days shorter when applying the IPBDA as compared to the standard method (3.8 and 5.2 weeks, respectively; 27% relative reduction). This was achieved mainly by reduced frequency (from 13.6 to 12.6%) and duration (from 5.7 to 5 weeks) of reoccurring events with grade ≥2 HFS. Consequently, treatment discontinuation due to grade ≥2 HFS was 7% less frequent with IPBDA than with the standard approach (21.6 and 23.2%, respectively). This gain in terms of HFS toxicity was achieved with maintaining equivalent efficacy to the standard method with 49.4% of responders with individualized dosage regimen as compared to the 49.2% of the standard regimen (Table 3). A clinical trial comparing the IPBDA and the standard methods should include 350 patients per arm to achieve at least 90% power to show a difference in grade ≥2 HFS duration at an alpha level of 0.05.

Sensitivity analysis concerning IPBDA details has been performed, investigating the impact of different target risks

(TR) (4, 5, 6%), of the lower limit for dose (25, 50% of the nominal dose), of the upper limit for dose (100, 125, 150%). Different times of starting dose increases were tested: after 2 or 4 cycles. As it is observed by clinicians that if HFS remains at grade 1 for a long time, the risk to develop to a higher grade is very low, so it was tested if allowing dose increase after at least 6 consecutive weeks with grade 1 would be beneficial. Other tried variations were: lower TR for increases than for reductions (2, 3%), lower TR for reductions if patient has tumor response (2, 3%) (only if 95th percentile of predicted tumor size at the next measurement (in 6 weeks) does not correspond to disease progression). The results of all these variations were in smaller or bigger extent inferior to those of the presented specification of IPBDA (data not shown).

Discussion

This work aimed at developing and investigating the solutions for a rational individual adaptation of anti-cancer drug doses according to side-effects evaluated on a categorical scale and at evaluating the impact of dose adjustments in terms of antitumor efficacy. In particular, the study dealt with the hand-and-foot syndrome induced by capecitabine and its tumor growth inhibition action as efficacy biomarker. An alternative to the standard empirical dose reduction protocol that would optimize the dosages individually based on toxicity risk predictions given by a longitudinal patient-specific HFS model was investigated. Virtual clinical trials were simulated to compare the different adaptation approaches and demonstrated that individual prediction-based dose adaptation (even using only grade-type data) was a feasible strategy for improving toxicity control during chemotherapy, without compromising the therapeutic efficacy. In comparison with the PK-guided methods [3–5], the presented method of dose adaptation based on toxicity grade has the advantages of neither requiring costly and constraining invasive measurements nor the assumptions about the relationships of plasma concentrations and the observed toxic outcome.

In this particular example, the benefit was rather small, but clinically significant. The statistical significance ($\alpha = 0.05$) is reached in at least 90% of studies with 350 patients per arm. The main obstacle for a stronger impact was the lack of sensitivity of the grade probabilities to the dose changes. HFS develops and reduces much slower than doses change. The sensitivity analysis of the model parameters indicated that due to the assumed accumulation of capecitabine (through the KPD model), the doses received during the preceding 3 weeks has a much lower impact on toxicity risk than do the total accumulated doses received, previous HFS grade, and individual random effects. Therefore, some patients are predisposed to experience the HFS and the therapeutic index shrinks quickly for them. In these cases, monitoring the toxicity risk serves to indicate the time when treatment with capecitabine should be discontinued and replaced by another therapy.

As dose adaptation can only be started after appearance of HFS, IPBDA could only reduce the frequency of reoccurring events with grade $\geq$2 HFS, but not of the first event. When a patient has grade 1 HFS, the predicted risk of HFS developing to the grade $\geq$2 is lower than when in grade 0, so dose reduction is less likely to be done.

In general, the rather low quality of empirical Bayes' estimates (EBEs) of individual random effects may reduce the efficacy of IPBDA. In studying this issue [20], it was shown that unbiased and precise EBEs can be obtained only in particularly favorable conditions, which were impossible to meet in the HFS case. In particular, effect saturation must be reached to correctly identify the E_{max} function parameters, within-subject distribution of grades should be close to uniform, and a high number of observations are needed as categorical data is information-poor. The quality of EBEs influences the quality of prediction of severe toxicity risk, and therefore the decisions concerning the dose adaptation. In extreme cases of the HFS example, the error in dose due to imprecision of EBEs could be 10-fold (data not shown). However, due to low sensitivity of HFS to dose changes, the impact of poor EBEs on the performance of dose adaptation was minimal (data not shown).

Some other limitations imposed by the employed HFS model may include not considering some possibly influential information about the pharmacokinetics, such as the activity of dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme for 5FU degradation [21]. Therefore, the approach presented here concerns only patients having no DPD deficiency.

Polymorphisms in genes coding for enzymes involved in transformation of capecitabine into 5FU have been associated with increased risk of severe HFS (cytidine deaminase [22]) and with better response and time to progression (carboxylesterase 2 [23]). Thymidylate synthase is a target enzyme for 5FU (and capecitabine, as its oral prodrug), polymorphisms in its gene have been associated with response to capecitabine in advanced colorectal cancer [24]. Methylenetetrahydrofolate reductase is a key enzyme in folate metabolism; polymorphisms in its gene have been related to toxicity rates with capecitabine [25]. Statistical associations were observed between polymorphisms in the transporter gene ATP-binding cassette B1 and a lower risk of HFS in capecitabine-treated patients [26]. Moreover, different amounts of folates in food were suggested as a possible explanation of regional differences in capecitabine tolerability [27]. The identified possible factors of

variability in efficacy and tolerability of capecitabine need further large well-designed studies to better determine their impact, and then could possibly be taken into account in dose adaptation schemes.

To enable extrapolation of the model-based dose adaptation algorithm to other dosing schedules, other cancer types and specific populations (prior therapy, performance status, age, sex, genotype, co-medications, etc.), mechanistic (physiologically based) models are needed.

The drawback of the Markov proportional odds model is that it is only a statistical description of dependence of the current week's toxicity grade on the previous week's toxicity grade; it does not rely on a physiological ground.

Furthermore, taking into account the possible uncertainty in grading might be suggested for future investigations in categorical data modeling, for example using hidden Markov chain model [28].

The adaptation method presented here determined the "best" dose according to a single HFS toxicity. Clinical benefit could be further improved by extending the method to address all frequent dose-limiting toxicities once their models are developed, and/or combined treatment protocols. The highest benefit of dose adaptations is expected to be achieved with reversible toxicities that have rapid kinetics, such as gastrointestinal ones.

This work constitutes the first application of an individualized dose adaptation of an anticancer drug based on a longitudinal mixed-effects dose-toxicity model for categorical observations. The proof of concept by clinical trial simulations represents the first step in the general approval in clinical practice of such an approach. Such virtual trials are particularly useful for assessing the possible impact of an investigational protocol and can be a valuable aid in decision-making concerning launching large, prospective, randomized clinical trials to validate the approach.

This work demonstrated the feasibility of individualized dose adaptation based on categorical endpoints and assessed its potential superiority to the standard empirical dose reductions via *in silico* clinical trials. Even in the case of the rather inert hand-and-foot syndrome induced by capecitabine, this new approach may enable clinically significant reduction in the duration of intolerable toxicity, as well as earlier detection of patients intolerant to the drug, without compromising drug efficacy on tumor shrinkage.

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