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Sequential designs for individualized dosing in phase I cancer clinical trials

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ABSTRACT

This paper addresses dose finding in clinical trials where individuals exhibit biologic characteristics that alter the toxicity risks of the individuals. In these situations, instead of determining a dose that works for every patient, the trial aims to identify a dosing algorithm that prescribes dose according to the patient's biomarker or pharmacokinetic expression. Specifically, we aim to dose patients around a pre-specified level of area under the curve of irinotecan concentration using the patients' baseline phenotypes that predict drug clearance. We propose least squares recursion procedures to estimate the dosing algorithm sequentially with an aim to treat patients in the trial around the true unknown dosing algorithm, and introduce a novel application of an eigenvalue theory that guarantees convergence to the true dosing algorithms. Our simulation study demonstrates that using an eigenvalue constraint improves the efficiency of the recursion by as large as 40%, while concentrating in-trial patient allocation around the true dosing algorithm. We also provide practical guidance on design calibration, and design future irinotecan studies based on data from our first trial.

1. Introduction

Phase I trials of a novel anticancer drug aim to determine a dose for further investigation in subsequent clinical studies. This dose is traditionally defined with respect to clinical toxicity. However, with the recent advances and increasing use of molecular targeted agents, it is often more relevant to use pharmacokinetic or biomarker expression as the basis of dose finding. Specifically, we are motivated by the use of irinotecan in patients with metastatic colorectal cancer [17]. Due to its metabolic mechanism, the expression and function of irinotecan is affected by numerous environmental and genetic factors, thus resulting in large variability in its pharmacokinetic property [12]. As a result, the conventional one-size-fits-all approach that prescribes a dose for all patients may not be appropriate and may result in overdosing, for instance, if a subject has low drug clearance. The basic idea of individualized dosing in early phase trials is to identify a dosing algorithm, as opposed to a single dose, based on an individual's baseline characteristics that are believed to alter susceptibility to the drug. For irinotecan, individualized dosing is made possible by the prediction of drug clearance using patient's phenotypes including γ-glutamyltransferase, midazolam activity, and height [14]. The rationale is that patients with higher predicted irinotecan clearance can tolerate and should receive higher dose, so as to reach a target plasma concentration. [17] consider individualized treatment of irinotecan based on a novel clearance prediction equation, and aim at a dose with expected area under the curve (AUC) of irinotecan at 22.157 μg × h/mL.

While the traditional dose finding studies utilize binary clinical toxicity as outcome, a large number of dose finding methodology for non-binary outcomes have been proposed in the literature to address a great variety of clinical situations, including the consideration of efficacy-toxicity tradeoff [3,15,21], the use of time-to-event outcomes [7], and the incorporation of pharmacokinetic parameters in predicting toxicity [13]. Several approaches have been proposed to target at the expected value of a continuous outcome as in the irinotecan study; see [1] and [8] for example. Furthermore, risk-specific dosing has been considered: [2] model toxicity as a continuous outcome within each risk group; [9] use bivariate isotonic regression to include risk and dose as covariates; [16] consider a Bayesian model for bivariate binary outcomes that uses probit models to depict the marginal dose-covariate-response relationships. Most of these risk-specific dosing methods, however, are not directly applicable to the irinotecan study where the covariate is continuous. Also, importantly, while the above-mentioned proposals vary in

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model assumptions and decision rules, they attempt to treat patients near the target dose. This type of approach, while ethically appealing, lacks theoretical justification. In case of a homogeneous population, [5] shows that applying the continual reassessment method with a multiparameter model may yield a dose sequence converging to a dose bounded away from the true target dose even if the model assumption is correct. The fundamental reason for this phenomenon is that the dose sequence depends on patient outcomes and is random. As such, there is no intrinsic mechanism to ensure that the design matrix will satisfy the conditions for desirable estimation properties. In this article, we propose a constrained least squares recursion procedure based on an eigenvalue theory that guarantees consistent estimation of the dosing algorithm.

In Section 2, we describe the irinotecan study data that motivate our model and method, and present the proposed method. In Section 3, we apply our method to design the next series of dose finding studies of irinotecan based on the data in [17], and discuss design calibration. The proposed method is illustrated and examined by simulation in Section 4. This article ends with a discussion in Section 5.

2. Methods

2.1. Notation and motivating data

van der Bol et al. [17] administer irinotecan as a single agent in 40 patients, with 20 patients dosed according to a clearance prediction equation (the "Equation arm") aiming to achieve a target AUC level of 22.157μg × h/mL in the patients, and the other 20 treated according to the conventional body surface area (BSA) formula:

$$x = \log(350) + b \tag{1}$$

where x denotes the logarithm of irinotecan dose and b is the BSA in logarithm. Patients in the Equation arm were dosed according to

$$x = t_0 + z, \tag{2}$$

where $t_0 = log(22.157)$ and z is the logarithm of the predicted clearance based on baseline phenotypes. This equation was derived based on a single compartment model stating that $y = x - z^*$ where y is the logarithm of irinotecan AUC and z^* is the true log-clearance of the patient. However, since z^* was not observable at baseline, the predicted value z was used as a proxy. More generally, the aim of this study was to estimate, for any given z, a patient-specific dose $\theta(z)$ so that $E(y|x,z) = t_0$. Under a simple linear model

$$E(y|x,z) = \alpha + \beta x + \gamma z, \tag{3}$$

the true dosing algorithm can be explicitly expressed as $\theta(z) = (t_0 - \alpha - \gamma z)/\beta$, while the Equation arm in [17] assumes the parameter values in the mean model known, namely $\alpha = 0, \beta = 1$, and $\gamma = -1$.

Fitting the irinotecan study data using least squares led to $\hat{\alpha} = 1.26$, $\hat{\beta} = 0.45$, and $\hat{\gamma} = -0.34$. A two-sided Wald's test for the hypothesis $\beta = 1$ gave $P = 0.055$ suggesting a possible deviation from the single compartment model, whereas the test for $\gamma = -1$ gave $P = 0.003$ indicating z was not a perfect proxy of z^*. Fig. 1 shows the dosing algorithms based on the least squares fit and the Equation arm, and suggests that the study subjects tended to receive lower doses than the least squares fit would otherwise prescribe.

The use of BSA values is particularly common to calculate doses of chemotherapy and has been well calibrated against other measurements such as weight. In the irinotecan study, the BSA values were available in all 40 patients, who had a mean of 1.9 m^2 and standard deviation of 0.22 m^2. This is comparable to the normative values [18]. Importantly, the BSA and predicted clearance are significantly associated; the correlation is 0.51 on their original scale, and 0.53 on log scale. This suggests that the predicted clearance and BSA are measuring similar attribute of an individual's metabolism.

2.2. Constrained least squares recursion

Motivated by the lack of fit due to the Equation arm(2), we seek to estimate the dosing algorithm under model (3) in a sequential manner in a dose-finding study. A common strategy to improve dose assignments for the study subjects takes a myopic approach that sets the next patient at the most recent estimate of $\theta(z)$. Specifically, we consider a least squares recursion (LSR) that aims to assign the $(n+1)$st patient with covariate z_{n+1} according to the least squares estimate of the dosing algorithm $\theta(z)$, that is, $\hat{\theta}_n(z_{n+1}) = (t_0 - \hat{\alpha}_n - \hat{\gamma}_n z_{n+1})/\hat{\beta}_n$, where $\left(\hat{\alpha}_n, \hat{\beta}_n, \hat{\gamma}_n\right)$ are the least squares estimates of (α, β, γ) using observations of the first n subjects. In practice, with clinical justification, we often set limits on the dose range, that is, we assign the $(n+1)$st patient at

$$x_{n+1} = \max\left[\min\left\{\hat{\theta}_n(z_{n+1}), x_{\max}\right\}, x_{\min}\right] \tag{4}$$

according to the LSR, where $x_{\min}$ and $x_{\max}$ delimit the dose range. This recursion can be viewed as an extension of the maximum likelihood recursion [20] with covariate adjustment. While this method intuitively puts study subjects at the current "best" dose, there is a lack of theoretical justification. Specifically, since the design points (x_i's) are chosen in a data-driven manner, there is no guarantee that the recursion will lead to consistent estimation of the model parameters and the dosing algorithm $\theta(z)$. To be precise, let M_n denote the design matrix of the first n study subjects, that is, the ith row of M_n is $(1, x_i, z_i)^T$, and let $\lambda_{\min}(n)$ and $\lambda_{\max}(n)$ respectively denote the minimum and maximum eigenvalues of $M_n^T M_n$. Under the recursion Eq. (4), the design matrix M_n is stochastic, under which [10] shows that consistency requires

$$\rho_n = \frac{\log \lambda_{\max}(n)}{\lambda_{\min}(n)} \to 0 \text{ a.s., as } n \to \infty. \tag{5}$$

We shall call ρ_n the eigenvalue ratio of the matrix $M_n^T M_n$ for brevity, although it is the ratio of $\log\lambda_{\max}(n)$ to $\lambda_{\min}(n)$. The eigenvalue condition (5) implies a weaker condition $\lambda_{\min}(n) \to \infty$ that in effect requires the design points to spread adequately apart. Since the myopic LSR does the exact opposite by concentrating dosing around a target dosing algorithm, it is conceivable that Eq. (5) may not hold; see Section 4 for an illustration. Thus, we propose applying LSR in conjunction with an eigenvalue constraint, thus called LSR-EVC. Precisely, we set the dose for the $(n+1)$st patient with baseline covariate z_{n+1} at $x_{n+1} = \max\left[\min\left\{\tilde{\theta}_n(z_{n+1}), x_{\max}\right\}, x_{\min}\right]$ where

$$\tilde{\theta}_n(z_{n+1}) = \arg\min_x \left|x - \hat{\theta}_n(z_{n+1})\right| \text{ subject to } \rho_{n+1}(x, z_{n+1}) \le r_{n+1} \tag{6}$$

and r_{n+1} is a prespecified sequence of positive real numbers converging to 0. The eigenvalue ratio $\rho_{n+1}(x, z_{n+1})$ is defined with respect to the matrix $V_{n+1}^T(x)V_{n+1}(x)$ for given x, where $V_{n+1}(x) = \left(M_n^T, (1, x, z_{n+1})^T\right)^T$. That is, $V_{n+1}(x_{n+1}) = M_{n+1}$ and $\rho_{n+1} = \rho_{n+1}(x_{n+1}, z_{n+1})$. Due to the eigenvalue constraint in Eq. (6), the sequence generated by LSR-EVC satisfies Eq. (5) by construct thus guaranteeing the consistency of $\hat{\theta}_n(z)$ for $\theta(z)$. Therefore, at the end of a study, we will use $\hat{\theta}_n(z)$ to estimate the dosing algorithm $\theta(z)$. During a study, the computation of $\tilde{\theta}_n(z_{n+1})$ can be easily done by a grid search that starts at $\hat{\theta}_n(z_{n+1})$ and iterates x away from $\hat{\theta}_n(z_{n+1})$ on a fine grid until the constraint is met. Both LSR and LSR-EVC are

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