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CANCER PHASE I CLINICAL TRIALS: EFFICIENT DOSE ESCALATION WITH OVERDOSE CONTROL

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SUMMARY

We describe an adaptive dose escalation scheme for use in cancer phase I clinical trials. The method is fully adaptive, makes use of all the information available at the time of each dose assignment, and directly addresses the ethical need to control the probability of overdosing. It is designed to approach the maximum tolerated dose as fast as possible subject to the constraint that the predicted proportion of patients who receive an overdose does not exceed a specified value. We conducted simulations to compare the proposed method with four up-and-down designs, two stochastic approximation methods, and with a variant of the continual reassessment method. The results showed the proposed method effective as a means to control the frequency of overdosing. Relative to the continual reassessment method, our scheme overdosed a smaller proportion of patients, exhibited fewer toxicities and estimated the maximum tolerated dose with comparable accuracy. When compared to the non-parametric schemes, our method treated fewer patients at either subtherapeutic or severely toxic dose levels, treated more patients at optimal dose levels and estimated the maximum tolerated dose with smaller average bias and mean squared error. Hence, the proposed method is promising alternative to currently used cancer phase I clinical trial designs. © 1998 John Wiley & Sons, Ltd.

1. INTRODUCTION

The primary purpose of a phase I clinical trial is to determine the dose of a new drug or therapeutic agent for use in a subsequent phase II trial. A long-accepted assumption underlying cancer therapy is that toxicity is a prerequisite for optimal antitumour activity.[1] Consequently, one must endure some degree of treatment related toxic reaction if patients are to have a reasonable chance of favourable response. Since higher doses are associated with both greater therapeutic benefits and an increased probability of severe toxic reaction, a cytotoxic drug should be administered at the maximum dose that cancer patients can tolerate. Consequently, the goal of a cancer phase I trial is to determine the highest dose associated with an acceptable level of toxicity. More precisely, the goal is to estimate the maximum tolerated dose (MTD), defined as the dose for which the probability of a medically unacceptable, dose-limiting toxicity (DLT) is

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equal to a specified value θ:

$$\text{Prob}\{\text{DLT}\,|\,\text{Dose} = \text{MTD}\} = \theta.$$

The value chosen for the target probability θ depends on the nature of the DLT; we would set it relatively high when the DLT is a transient, correctable or non-fatal condition, and low when it is lethal or life threatening.

Representing the first application of a proposed drug to humans, the phase I trial constitutes one of the most important steps in the drug's development.[2] Since initial experience with a new agent may unduly influence its fate, a careful and thoughtful approach to the design of phase I trials is essential. Unfortunately, clinical research involving humans poses serious ethical problems and clinical trials involving oncology patients and cytotoxic drugs have been among the most problematic of all.[3] In contrast to other phase I trials, cancer phase I trials have a therapeutic aim. Typically, participants in a cancer phase I trial are patients at advanced disease stages who consent to participate in the trial only as a last resort in seeking cure. Thus, from a therapeutic perspective, one should design cancer phase I trials to minimize both the number of patients treated at low, non-therapeutic doses as well as the number given severely toxic overdoses.

In the next section we describe a dose escalation scheme that controls the probability a patient will receive an overdose. The scheme, referred to as EWOC (escalation with overdose control), is Bayesian-feasible of level $1 - \alpha$ as defined by Eichhorn and Zacks.[4] That is, EWOC selects a dose level for each patient so that the predicted probability the dose exceeds the MTD is less than or equal to a specified value α. Zacks *et al.*[5] showed that among designs that are Bayesian-feasible of level $1 - \alpha$, EWOC is optimal in the sense that it minimizes the predicted amount by which any given patient is underdosed. Thus, EWOC is designed to approach the MTD as rapidly as possible subject to the constraint that the predicted proportion of patients given an overdose is less than or equal to α.

2. METHOD

The key concept underlying EWOC is that one can select dose levels for use in a phase I trial so that the predicted proportion of patients who receive an overdose is equal to a specified value α, called the feasibility bound. This is accomplished by computing, at the time of each dose assignment, the posterior cumulative distribution function (CDF) of the MTD. For the kth dose assignment the posterior CDF of the MTD is the function π_k given by

$$\pi_k(\gamma) = \text{Prob}\{\text{MTD} \leqslant \gamma\,|\,\mathscr{D}_k\}$$

where $\mathscr{D}_k$ denotes the data at the time of treatment for the kth patient and would include for each previously treated patient the dose administered, the highest level of toxicity observed and any relevant covariate measurements. $\pi_k(\gamma)$ is the conditional probability that γ is an overdose given the data currently available. Based on this, EWOC selects for the kth patient the dose level x_k such that

$$\pi_k(x_k) = \alpha.$$

That is, we select the dose for each patient so that the predicted probability it exceeds the MTD is equal to α.

In the next section we describe EWOC for the specific case where toxicity is measured on a binomial scale (presence or absence of DLT), there are no known covariates and one plans to accrue a fixed number n of patients to the trial. Extensions of EWOC to accommodate more informative response measures, covariate information and variable sample sizes are currently under investigation. In Section 2.2 we present an example illustrating the application of EWOC to a cancer phase I clinical trial involving 5-fluorouracil.

2.1. Dose escalation method

Let $X_{\min}$ and $X_{\max}$ denote the minimum and maximum dose levels available for use in the trial. One chooses these dose levels in the belief that $X_{\min}$ is safe when administered to humans and

$$X_{\min} \leqslant \text{MTD} \leqslant X_{\max}. \tag{1}$$

The dose for the first patient is $X_{\min}$ and we shall select only dose levels between $X_{\min}$ and $X_{\max}$ for use in the trial. Thus, if x_i denotes the dose level selected for the ith patient, $i = 1, \ldots, n$, then

$$x_1 = X_{\min}$$

and

$$x_i \in [X_{\min}, X_{\max}], \forall i = 1, \ldots, n.$$

We model the relationship between dose level and toxicity as

$$\text{Prob}\{\text{DLT} \mid \text{Dose} = x\} = F(\beta_0 + \beta_1 x) \tag{2}$$

where F is a specified distribution function, called a tolerance distribution, and β_0 and β_1 are unknown. We assume that $\beta_1 > 0$ so that the probability of a DLT is a monotonic increasing function of dose. The MTD is the dose level, denoted γ, such that the probability of a DLT is θ. It follows from (2) that

$$\gamma = \frac{F^{-1}(\theta) - \beta_0}{\beta_1}$$

$$= X_{\min} + \frac{F^{-1}(\theta) - F^{-1}(\rho_0)}{\beta_1}$$

where ρ_0 denotes the probability of a DLT at the starting dose $x_1 = X_{\min}$. Figure 1 illustrates a typical dose-toxicity model.

Denote by y_i the response of the ith patient where $y_i = 1$ if a DLT is manifest and $y_i = 0$, otherwise. The data after observation of k patients is $\mathscr{D}_k = \{(x_i, y_i), i = 1, \ldots, k\}$ and the likelihood function of (β_0, β_1) given $\mathscr{D}_k$ is

$$L(\beta_0, \beta_1 \mid \mathscr{D}_k) = \prod_{i=1}^{k} F(\beta_0 + \beta_1 x_i)^{y_i} [1 - F(\beta_0 + \beta_1 x_i)]^{1 - y_i}.$$

We incorporate prior information about β_0 and β_1 through a prior probability density function $h(\beta_0, \beta_1)$ defined on

$$\Omega = \{(a, b) \in \Re^2 : b > 0, F(a + bX_{\min}) \leqslant \theta \leqslant F(a + bX_{\max})\}. \tag{3}$$

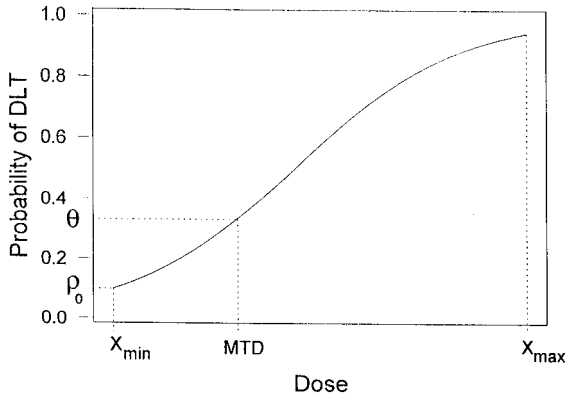

Figure 1. The probability of DLT as a function of dose

After an application of Bayes theorem, the joint posterior distribution of (β_0, β_1) given the data $\mathscr{D}_k$ is

$$\mathscr{P}(\beta_0, \beta_1 | \mathscr{D}_k) = \tau^{-1} L(\beta_0, \beta_1 | \mathscr{D}_k) h(\beta_0, \beta_1) I_\Omega(\beta_0, \beta_1) \tag{4}$$

where

$$\tau = \iint_\Omega L(x, y | \mathscr{D}_k) h(x, y) \mathrm{d}x \, \mathrm{d}y$$

and I_Ω denotes the indicator function for the set Ω. We can derive the marginal posterior cumulative distribution function of the MTD given $\mathscr{D}_k$ from (4) through the transformation $T(\beta_0, \beta_1) = (\rho_0, \gamma)$. Denoting the image of Ω under the transformation T by $T(\Omega)$, it follows from (1) and (3) that

$$T(\Omega) = [0, \theta] \times [X_{\min}, X_{\max}].$$

The inverse transformation is

$$T^{-1}(\rho_0, \gamma) = (f_1(\rho_0, \gamma), f_2(\rho_0, \gamma))$$

where the functions f_1 and f_2 are defined on $T(\Omega)$ by

$$f_1(\rho_0, \gamma) = \frac{\gamma F^{-1}(\rho_0) - X_{\min} F^{-1}(\theta)}{\gamma - X_{\min}}$$

and

$$f_2(\rho_0, \gamma) = \frac{F^{-1}(\theta) - F^{-1}(\rho_0)}{\gamma - X_{\min}}.$$

We can now write the joint posterior probability density function (PDF) of (ρ_0, γ) given $\mathscr{D}_k$ as

$$P(\rho_0, \gamma | \mathscr{D}_k) = \tau^{-1} L(f_1(\rho_0, \gamma), f_2(\rho_0, \gamma) | \mathscr{D}_k) g(\rho_0, \gamma)$$

where

$$g(\rho_0, \gamma) = h(f_1(\rho_0, \gamma), f_2(\rho_0, \gamma)) f_2(\rho_0, \gamma) \left[\frac{\partial}{\partial p} F^{-1}(p) \Big|_{p = p_0} \right] I_{T(\Omega)}(\rho_0, \gamma).$$

Note that g is the prior PDF induced for (ρ_0, γ) by the choice of h as the prior PDF of (β_0, β_1). Elicitation of prior information can be through specification of the PDF g directly, rather than through the choice of h. This might be advantageous since γ is the parameter of interest and one often conducts preliminary studies at or near the starting dose so that one can select a meaningful informative prior for ρ_0. Letting

$$\Theta(\gamma) = \{\rho_0 : (\rho_0, \gamma) \in T(\Omega)\}$$

we can write the marginal posterior PDF of the MTD given $\mathscr{D}_k$ as

$$\pi(\gamma \mid \mathscr{D}_k) = \iint_{\Theta(\gamma)} P(\rho_0, \gamma \mid \mathscr{D}_k) \, \mathrm{d}\rho_0.$$

The marginal posterior CDF of the MTD given $\mathscr{D}_k$ is then

$$\pi_k(z) = \int_{X_{\min}}^{z} \pi(\gamma \mid \mathscr{D}_k) \, \mathrm{d}\gamma, \; x \in [X_{\min}, X_{\max}].$$

We can now describe EWOC as follows. The first patient, or cohort of patients, receives the dose $x_1 = X_{\min}$. We select the dose for each subsequent patient so that on the basis of all the available data the posterior probability that it exceeds the MTD is equal to the feasibility bound α. Hence, the kth patient receives the dose

$$x_k = \pi_{m(k)}^{-1}(\alpha) \qquad K = 2, \ldots, n, \tag{5}$$

where $m(k)$ denotes the number of observations available at the time of treatment for the kth patient.

The dose sequence defined by (5) assumes that all dose levels between $X_{\min}$ and $X_{\max}$ are available for use in the trial. However, due to practical and physical constraints, phase I clinical trials are typically based on a small number of prespecified dose levels. In such cases we select for the kth patient the dose level

$$D_k = \max\{d_1, \ldots, d_r : d_i - x_k \leqslant T_1 \text{ and } \pi_k(x_k) - \alpha \leqslant T_2\} \tag{6}$$

where $d_1, \ldots, d_r$ are the dose levels chosen for experimentation and T_1 and T_2 are prespecified non-negative real numbers we refer to as tolerances. We note that the dose sequence given by (6) is Bayesian-feasible of level $1 - \alpha$ if and only if at least one of the tolerances T_1 and T_2 is equal to zero. Positive tolerances would be chosen to permit the use of dose levels above yet sufficiently close to the optimal Bayesian-feasible dose x_k.

Since cancer patients often exhibit delayed response to treatment, the time required to resolve toxicity can be longer than the average time between successive accruals. Consequently, new patients frequently become available to the study before we have observed the responses of all previously treated patients. It is therefore important to note that EWOC does not require that we know all patient responses before we can treat a newly accrued patient. Instead, we can select the dose for the new patient on the basis of the data currently available.

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