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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

$$\begin{aligned}\gamma &= \frac{F^{-1}(\theta) - \beta_0}{\beta_1} \\ &= X_{\min} + \frac{F^{-1}(\theta) - F^{-1}(\rho_0)}{\beta_1}\end{aligned}$$

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

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

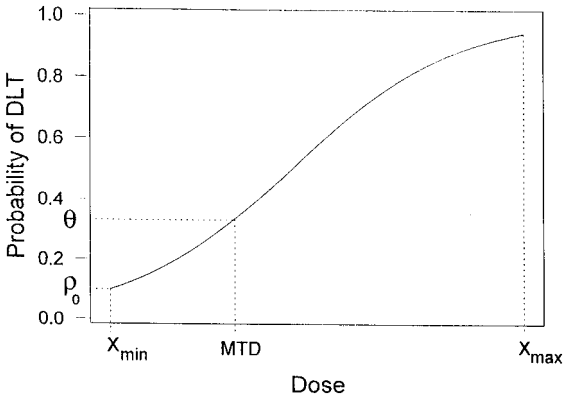

Figure 1. The probability of DLT as a function of dose

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

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

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.

Upon completion of the trial we can estimate the MTD by minimizing the posterior expected loss with respect to some choice of loss function l. Thus, the dose recommended for use in a subsequent phase II trial is the estimate $\hat{\gamma}_l$ such that

$$\int_{X_{\min}}^{X_{\max}} l(\hat{\gamma}_l, \gamma)\pi(\gamma \mid \mathscr{D}_n)\,\mathrm{d}\gamma \leqslant \int_{X_{\min}}^{X_{\max}} l(x, \gamma)\pi(\gamma \mid \mathscr{D}_n)\,\mathrm{d}\gamma \quad \forall x \in [X_{\min}, X_{\max}].$$

Candidate estimators include the mean, median and mode of the marginal posterior PDF of the MTD. One should consider asymmetric loss functions since underestimation and overestimation have very different consequences. Indeed, the dose x_k selected by EWOC for the kth patient corresponds to the estimate of the MTD having minimal risk with respect to the asymmetric loss function

$$l_\alpha(x, \gamma) = \begin{cases} \alpha(\gamma - x) & \text{if } x \leqslant \gamma \text{ that is, if } x \text{ is an underdose} \\ (1 - \alpha)(x - \gamma) & \text{if } x > \gamma \text{ that is, if } x \text{ is an overdose.} \end{cases} \tag{7}$$

Note that the loss function l_α implies that for any $\delta > 0$, the loss incurred by treating a patient at δ units above the MTD is $(1 - \alpha)/\alpha$ times greater than the loss associated with treating the patient at δ units below the MTD. This interpretation might provide a meaningful basis for the selection of the feasibility bound.

We note that we can estimate the MTD using a different prior PDF than that used to design the phase I trial.[6] Furthermore, some authors (for example, Watson and Pelli[7]) have suggested use of Bayesian scheme to design the trial and use of maximum likelihood to estimate the MTD.

2.2. Example

EWOC was used to design a phase I clinical trial that involved the antimetabolite 5-fluorouracil (5-FU). In this trial a total of $n = 12$ patients with malignant solid tumours are to be treated with a combination of 5-FU, leucovorin and topotecan. The goal is to determine the dose level of 5-FU that, when administered in combination with fixed levels of the other two agents (20 mg/m^2 leucovorin, 0.5 mg/m^2 topotecan), results in a probability of $\theta = 1/3$ that a grade 4 hematologic or grade 3 or 4 non-hematologic toxicity is manifest within two weeks.

Since preliminary studies indicated that 140 mg/m^2 of 5-FU was well tolerated when given concurrently with up to 0·5 mg/m^2 of topotecan, this level was selected as the starting dose for the phase I trial. Hence

$$X_{\min} = 140.$$

Furthermore, a previous trial involving 5-FU alone estimated the MTD as 425 mg/m^2. Since a given level of 5-FU has been observed to be more toxic when given in conjunction with topotecan than when administered alone, the MTD of 5-FU in combination with leucovorin and topotecan is believed to be below 425 mg/m^2, the single agent MTD. Consequently, the maximum allowed dose for the phase I trial is

$$X_{\max} = 425.$$

Simulations and prior experience have shown EWOC to perform well when we take the tolerance distribution as the logistic and the prior PDF used for (ρ_0, γ) is the uniform distribution. Hence, we modelled the relationship between dose-limiting toxicity and the dose

level of 5-FU as

$$\text{Prob}\{\text{DLT}\,|\,\text{Dose} = x\} = \frac{\exp\{\beta_0 + \beta_1 x\}}{1 + \exp\{\beta_0 + \beta_1 x\}}$$

and we took the joint prior PDF of (ρ_0, γ) as

$$g(\rho_0, \gamma) = 57^{-1} I_{[0,0{\cdot}2]\times[140,425]}(\rho_0, \gamma).$$

It follows that the marginal posterior CDF of the MTD at the time of the kth dose assignment is

$$\pi_k(x) = \int_{140}^{x} \int_{0}^{0{\cdot}2} \mathscr{P}(\rho_0, \gamma\,|\,\mathscr{D}_{m(k)})\,\mathrm{d}\rho_0\,\mathrm{d}\gamma$$

where

$$\mathscr{P}(\rho_0, \gamma\,|\,\mathscr{D}_k) = \tau^{-1} \frac{\prod_{i\in S(k)}^{m(k)} \exp\{f(\rho_0, \gamma\,|\,x_i)\}}{\prod_{i=1}^{m(k)} [1 + \exp\{f(\rho_0, \gamma\,|\,x_i)\}]} I_{[0,0{\cdot}2]\times[140,425]}(\rho_0, \gamma)$$

with

$$\tau = \int_{T(\Omega)} \int \prod_{i\in S(k)} \exp\{f(\rho_0, \gamma\,|\,x_i) \prod_{i=1}^{m(k)} [1 + \exp\{f(\rho_0, \gamma\,|\,x_i)\}]^{-1}\,\mathrm{d}\rho_0\,\mathrm{d}\gamma$$

$$f(\rho_0, \gamma\,|\,x) = \frac{\log\left(\dfrac{\rho_0}{1-\rho_0}\right)(\gamma - x) + \log\left(\dfrac{\theta}{1-\theta}\right)(x - X_{\min})}{\gamma - X_{\min}}$$

and

$$S(k) = \{i = 1, \ldots, m(k) : y_i = 1\}.$$

For this trial the feasibility bound is equal to

$$\alpha = 0{\cdot}25$$

this value being a compromise between the therapeutic aim of the trial and the need to avoid treatment attributable toxicity. Consequently, escalation of 5-FU between successive patients is to the estimated dose level that falls below the MTD with 75 per cent confidence. The first patient accrued to the trial receives the dose $x_1 = 140\ \text{mg/m}^2$. If the first patient exhibits DLT, we will have violated the assumption that the initial dose is safe and we would suspend the trial (to restart at a lower initial dose or to terminate at the discretion of the principal investigator). Otherwise, we dose the next four patients according to the schedule given in Figure 2.

3. SIMULATION COMPARISONS

We conducted a simulation study to compare the performance of EWOC with seven phase I dose escalation schemes consisting of four up-and-down (UD) designs, two stochastic approximation (SA) methods and a Bayesian scheme known as the continual reassessment method (CRM). We compared the methods with respect to the proportion of patients assigned dose levels above and

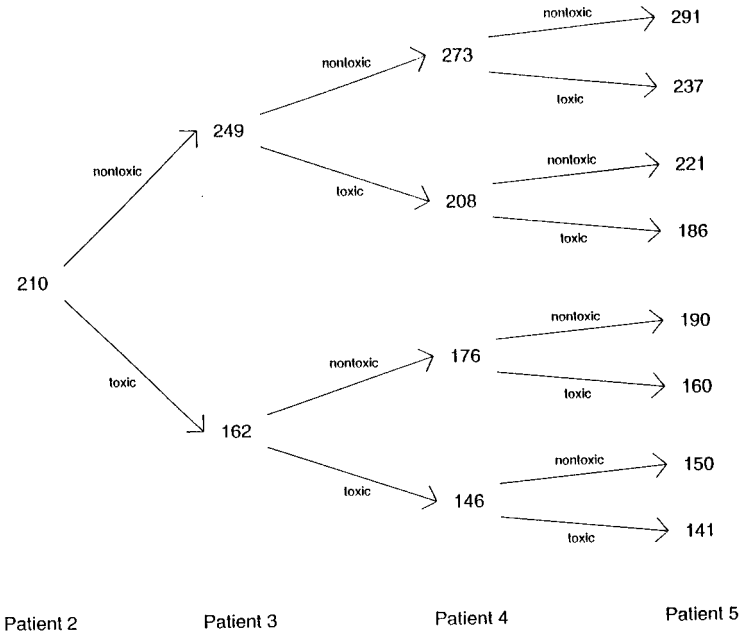

Figure 2. The dose level to be given each of patients 2 to 5 in the 5-FU trial contingent on the doses and responses of preceding patients

below the MTD, the proportion of patients exhibiting DLT and the bias and mean squared error observed for the estimator of the MTD.

In cancer research the vast majority of phase I trials are based on UD dose escalation designs.[8–11] With these methods, dose escalation proceeds either through a small number of preselected dose levels or via prespecified increments typically based on a modified Fibonacci sequence. The four designs considered in this study were proposed by Storer[10] and are described as follows:

*UD*1. Treat patients in cohort groups that consist of three patients each of whom receives the same dose. If no DLT is observed at a given dose level, then the next cohort receives the next highest dose. Otherwise, the next cohort is treated at the same dose and the trial then either continues at the next highest dose if exactly one of the last six patients exhibit DLT or terminates with observation of 2 or more DLT.

*UD*2. Treat patients in cohorts of size three. Escalate the dose if no DLT is observed, de-escalate if more than one patient manifests DLT or repeat the dose if exactly one patient exhibits dose limiting toxicity. The trial continues until observation of a specificied number n of patients.

*UD*3. Treat patients one at a time. De-escalate the dose with each DLT and escalate it after two consecutive non-toxic responses. The trial continues until observation of a specified number n of patients.

*UD*4. Treat patients one at a time. Escalate the dose continuously until observation of the first DLT. Thereafter implement design UD3.

Various authors[12–16] have proposed designs for phase I clinical trials based on the stochastic approximation methods of Robbins and Monro.[17] With these designs patients are assigned doses according to

$$x_{j+1} = x_j - a_j(y_j - \theta)$$

where $\{a_j\}_{j=1}^{\infty}$ is a sequence of positive real numbers such that $a_j \to 0$ as $j \to \infty$. The two SA methods considered in this simulation study correspond to the sequences

$$\text{SA1: } a_j = \frac{1}{2j}$$

and

$$\text{SA2: } a_j = \frac{1}{jb_j}$$

where

$$b_j = \begin{cases} 2 & \text{if } \displaystyle\sum_{i=1}^{j} x_i y_i - \left(\sum_{i=1}^{j} x_i\right)\left(\sum_{i=1}^{j} y_i\right)\Big/ j = 0 \\ \dfrac{\displaystyle\sum_{i=1}^{j} x_i y_i - \left(\sum_{i=1}^{j} x_i\right)\left(\sum_{i=1}^{j} y_i\right)\Big/ j}{\displaystyle\sum_{i=1}^{j} x_i^2 - \left(\sum_{i=1}^{j} x_i\right)^2\Big/ j} & \text{otherwise.} \end{cases}$$

O'Quigley *et al.*[18] proposed a Bayesian dose escalation scheme referred to as the continual reassessment method (CRM). In its original formulation we describe CRM as follows. Specify a model for the dose–toxicity relationship and, at each stage of the trial, obtain a Bayesian estimate of the MTD using all the data then available. Choose the dose recommended for each patient from a prespecified discrete set of levels as close as possible to the estimate of the MTD. We simulated a modification of this scheme wherein we treat each patient at the mean of the marginal posterior PDF of the MTD. Note that the dose assigned to each patient by this scheme corresponds to the estimate of the MTD having minimal risk with respect to squared error loss, whereas the dose assigned by EWOC is chosen to minimize risk with respect to the asymmetric loss function given by (7).

3.1. Simulation set-up

Throughout the simulations we generated the data according to the logistic model

$$\Pr\{\text{DLT} \mid \text{Dose} = x\} = \frac{\exp\left\{\ln\left[\dfrac{\rho_0}{1-\rho_0}\right] + \ln\left[\dfrac{\theta(1-\rho_0)}{\rho_0(1-\theta)}\right]\dfrac{x}{\gamma}\right\}}{1 + \exp\left\{\ln\left[\dfrac{\rho_0}{1-\rho_0}\right] + \ln\left[\dfrac{\theta(1-\rho_0)}{\rho_0(1-\theta)}\right]\dfrac{x}{\gamma}\right\}}$$

with ρ_0 assuming each of the values 0·05, 0·10 and 0·15, and the MTD taking on both of the values $\gamma = 0{\cdot}3$ and $\gamma = 0{\cdot}5$. Thus, we considered six cases corresponding to the six distinct combinations

of ρ_0 and γ. We assumed that dose levels were standardized so that the starting dose for each trial was the standardized dose $x_1 = 0$ and all subsequent dose levels were selected from the unit interval. Since the performance of the UD designs depends on the dose levels available for use in the trial, we simulated each UD method using both of $\{0(0{\cdot}2)1\}$ and $\{0(0{\cdot}1)1\}$ as the set of preselected dose levels. Furthermore, since Storer[10] constructed the UD designs for the specific choice of target probability $\theta = 1/3$, we used that value of θ in all simulation runs.

When simulating the Bayesian schemes, EWOC and CRM, we held the feasibility bound fixed at $\alpha = 0{\cdot}25$, we assumed that ρ_0 and the MTD were independent *a priori* and we took the marginal prior PDF of the MTD as the uniform on the unit interval. To select a prior PDF for ρ_0, we performed preliminary simulations to examine the performance of the two schemes when the prior for ρ_0 was either

$$P_0 : \text{the uniform on } [0, \theta]$$

or

$$P_\varepsilon : \text{the uniform on } [\rho_0, \rho_0 + \varepsilon], \quad \varepsilon \in (0, \theta - \rho_0).$$

The results showed that for each selected value of ε both CRM and EWOC exhibited more rapid dose escalation when we used P_ε instead of P_0 as the prior PDF. Furthermore, if for a given set of $i-1$ observations $x_i(\varepsilon)$ denotes the dose recommended by EWOC for the ith patient when the prior PDF of ρ_0 is P_ε, then it can be shown that $x_i(\varepsilon_1) \geqslant x_i(\varepsilon_2)$, $\forall \varepsilon_1 < \varepsilon_2$. Consequently, for the class of priors considered here, the proportion of patients overdosed by EWOC is maximized if the ith patient is assigned the dose $x_i = \lim_{\varepsilon \to 0} x_i(\varepsilon)$, corresponding to the recommended dose under the assumption that ρ_0 is known. Since the primary purpose of the simulation study was to compare the dose escalation schemes with respect to the frequency and magnitude of overdosing, we simulated both CRM and EWOC under the assumption that the probability of a dose-limiting toxicity at the starting dose was known. That is, to avoid conferring the model based schemes with an unfair advantage, we simulated EWOC and CRM under conditions unfavourable to them.

Upon completion of each UD, SA and CRM trial we estimated the MTD as $\hat{\gamma} = x_{n+1}$, that is, as the dose level that we would have given the next patient had we allowed the trial to continue. This is the estimate typically used in practice. For the UD schemes it generally corresponds to the highest dose for which the observed proportion of DLTs was below θ, while for CRM it has minimal risk with respect to squared error loss. A theoretical basis for the use of this estimate with the SA schemes is provided by the fact that x_n converges almost surely to the MTD under rather general conditions.[19] For CRM the estimate $\hat{\gamma} = x_{n+1}$ is the marginal posterior mean of γ given $\mathscr{D}_n$. Hence, for the purpose of comparison, we used the posterior mean of γ as the estimate of the MTD after each simulated EWOC trial. Furthermore, to determine whether the non-parametric schemes might compare more favourably to the Bayesian schemes if we had employed a model based estimate of the MTD, we used the posterior mean of γ to obtain a second estimate of the MTD after each UD trial.

For each of the six combinations considered for ρ_0 and γ, we simulated a total of 10,000 trials for each of the UD and SA designs while, due to their computational complexity, we simulated only 2000 trials for each of EWOC and CRM. Each simulated trial consisted of $n = 24$ patients for each of the fixed sample size methods (all but UD1) and a maximum of 30 patients for the variable length scheme UD1.

3.2. Results

In Figures 3 to 12 we compare the dose escalation schemes on the basis of the proportion of patients treated at selected dose levels and with respect to the efficiency with which they estimated the MTD. For Figures 3 to 5 and 7 to 12, each point represents the results observed for one of the six selected combinations of ρ_0 and γ, with the results obtained for $\gamma = 0{\cdot}3$ being depicted as a + and those for $\gamma = 0{\cdot}5$ as a $\times$. To facilitate comparison, we show the average of the six results observed for each scheme (depicted as a $\bullet$) and we have drawn a reference line through the average of the results obtained for EWOC. For each of the UD schemes we show the results obtained using the dose set $\{0(0{\cdot}2)1\}$ to the left of those obtained the dose set $\{0(0{\cdot}1)1\}$.

Figure 3 depicts the proportion of patients treated at dose levels for which the probability of a toxic response was less than 0·2. These patients were treated at dose levels where the drug is relatively inactive and therefore potentially non-therapeutic. The results indicate that EWOC treated fewer patients at low, possibly subtherapeutic, dose levels than did any of the nonparametric schemes. However, for each of the six selected combinations of ρ_0 and γ, we observed that EWOC treated more patients at the low dose levels than did CRM. This is expected since EWOC attempts to protect patients from being overdosed and so tends to treat patients at lower dose levels than does CRM.

Figure 4 displays the proportion of patients treated at dose levels for which the probability of a toxic response was less than the target probability θ but greater than 0·2. We describe these dose levels as optimal in the sense of being near but not above the MTD. The results show that the overall proportion of patients treated at optimal dose levels was higher for EWOC than it was for any of the other seven dose allocation schemes. Furthermore, for each of the six selected combinations of ρ_0 and γ, EWOC treated more patients at favourable dose levels than any of the other methods considered in this study except SA2.

Figure 5 shows the proportion of patients treated at dose levels above the MTD. The overall proportion of patients overdosed by EWOC was 0·193, slightly below the selected feasibility bound $\alpha = 0{\cdot}25$. For each of the six cases considered, EWOC overdosed a smaller proportion of patients than did CRM and compared favourably with SA1 and the UD schemes based on 6 dose levels. EWOC tended to overdose patients at a higher rate than SA2 and the UD schemes based on 11 dose levels. However, the latter schemes were overly conservative, treating a large proportion of patients at extremely low dose levels. Note that by choosing smaller values of α it is possible to reduce the proportion of patients overdosed by EWOC to levels that are comparable to those observed for any of the nonparametric designs. Figure 6 provides an indication of the extent to which EWOC afforded protection from overdosing relative to CRM, for the particular case where $P_1 = 0{\cdot}1$ and $\gamma = 0{\cdot}3$. There, we can see that EWOC treated only 31 per cent of the patients at dose levels above the MTD, while CRM overdosed nearly twice as many. Relative to CRM, EWOC can have a substantial impact on the level of overdosing in a phase I clinical trial.

Figure 7 shows the proportion of patients treated at dose levels for which the probability of a toxic response exceeded 0·5. These results show that EWOC subjected fewer patients to these severely toxic doses than did any of the other methods except SA2. When the MTD was equal to 0·5, CRM treated over three times as many patients at unacceptably high dose levels as EWOC. Overall, EWOC treated fewer patients at dose levels significantly above the target MTD.

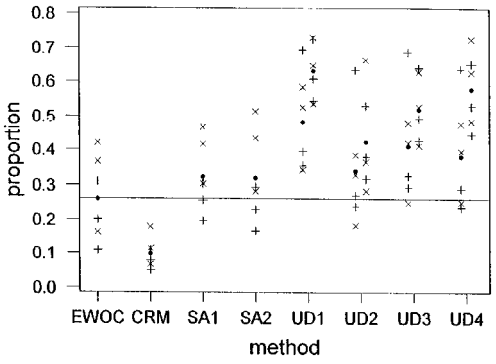

Figure 3. Proportion of patients given doses for which the probability of a severe toxic reaction is less than or equal to 1/5. Each × and + represents the results from all simulation runs for a particular parameter combination. Each point, (●), is the average of the results obtained for a particular method at the six parameter combinations considered. For each of the UD schemes the results obtained when only 6 dose levels were used are shown to the left of the results obtained when 11 levels were used

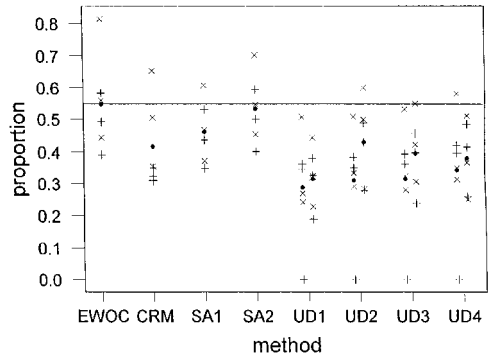

Figure 4. Proportion of patients given dose levels for which the probability of a severe toxic reaction is greater than 1/5 but not greater than the target probability $\theta = 1/3$ (see Figure 3 for symbol definitions)

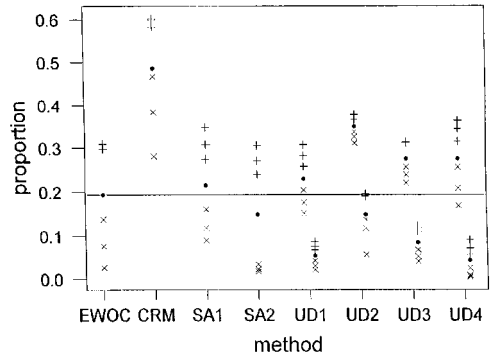

Figure 5. Proportion of patients given dose levels above the MTD (see Figure 3 for symbol definitions)

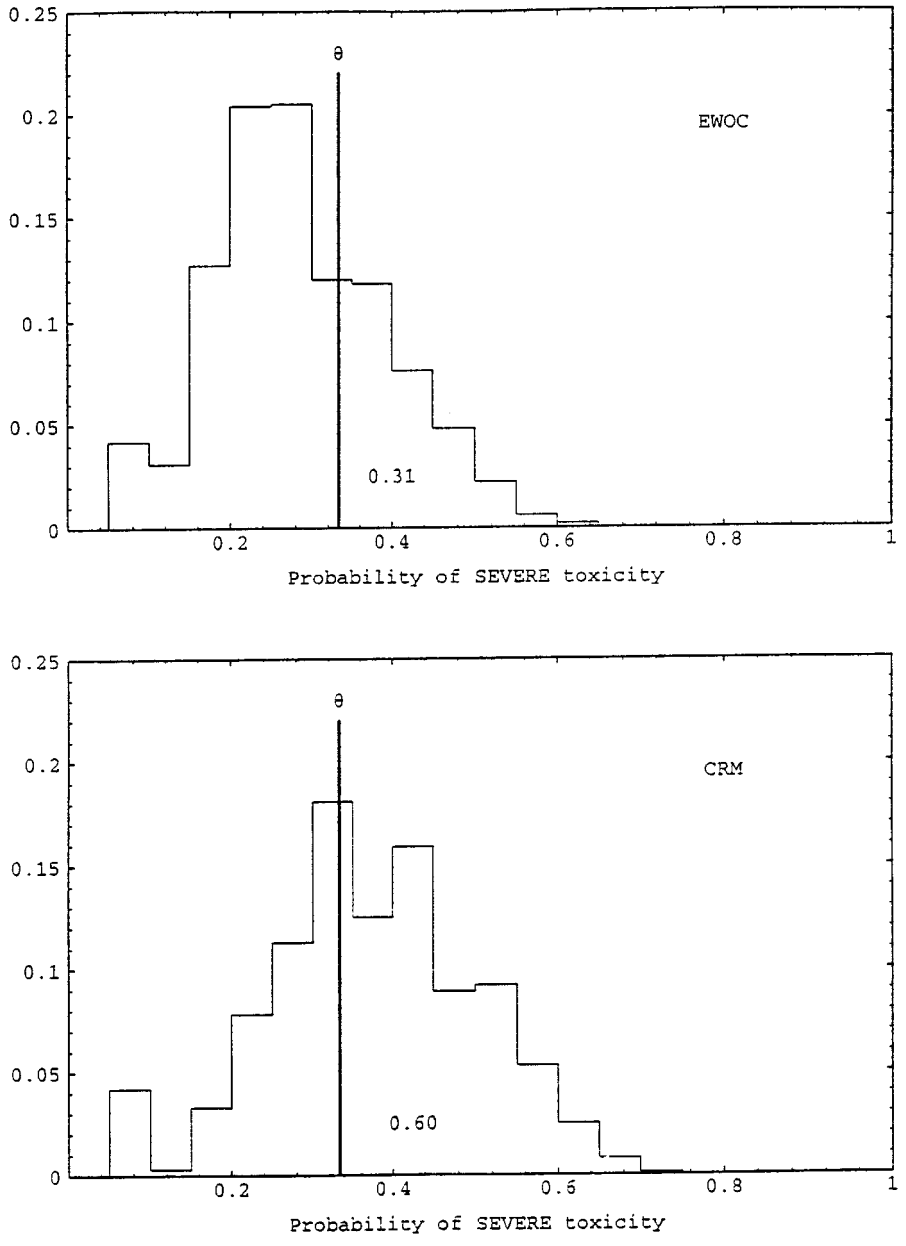

Figure 6. Histograms of the probability of toxic response for the dose levels selected by CRM and EWOC. For the intervals [0, 0·05), [0·05, 0·1), … , [0·9, 0·95), [0·95, 1·0] each histogram shows the proportion of patients given a dose level such that the probability of a severe toxic reaction is contained in that interval. The number in the body of each histogram in the proportion of patients given a dose level above the MTD

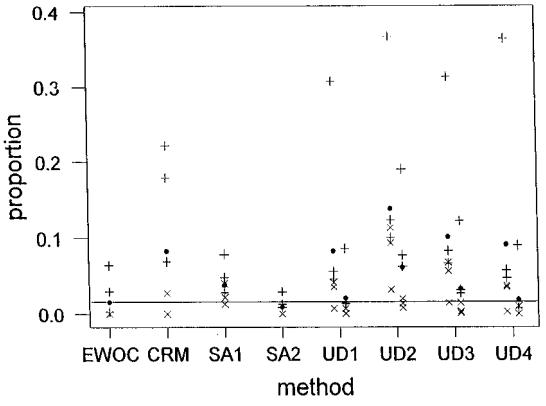

Figure 7. Proportion of patients given dose levels for which the probability of a severe toxic reaction was greater than 1/2 (see Figure 3 for symbol definitions)

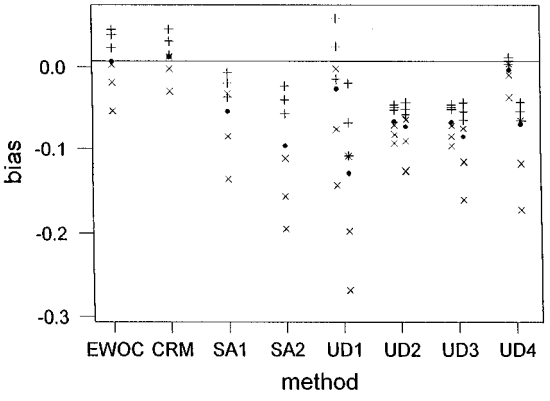

Figure 8. Average bias of $\hat{\gamma}$, the estimate of the MTD (see Figure 3 for symbol definitions)

Figures 8 to 11 compare the dose escalation schemes with respect to the efficiency of $\hat{\gamma}$, the estimator of the MTD. The bias observed for each estimator (computed as $\hat{\gamma} - \gamma$) is shown in Figures 8 and 9 and the root mean squared error ($\sqrt{\text{MSE}}$) in Figures 10 and 11. In Figures 8 and 10 the results are given for the non-parametric schemes when the MTD was estimated as the last recommended dose (that is, $\hat{\gamma} = x_{n+1}$). Figures 9 and 11 compare the results obtained for EWOC and the UD schemes when the MTD was estimated as the mean of the marginal posterior distribution of γ. All of the non-parametric methods tended to provide significantly biased estimates of the MTD while the overall mean bias associated with both of the Bayesian schemes was near zero. With respect to both bias and $\sqrt{\text{MSE}}$, EWOC provided more efficient estimates of the MTD than did any of the non-parametric methods. However, for each of the six cases considered, CRM estimated the MTD with smaller $\sqrt{\text{MSE}}$ than did EWOC. This was anticipated, because by construction CRM should tend to select dose levels closer to the MTD, allowing more efficient estimation. Thus, a slight decrease in the accuracy of the MTD estimate is the price one pays for incorporation into EWOC of protection from overdosing.

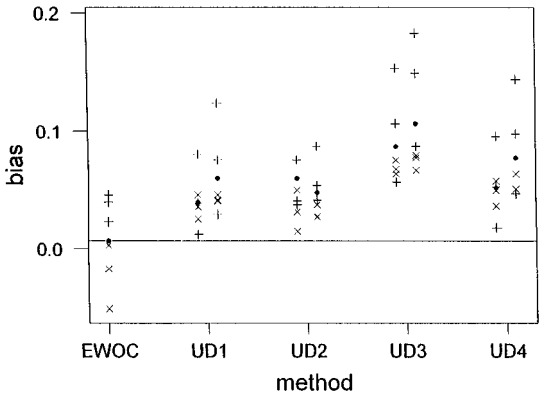

Figure 9. Average bias of $\hat{\gamma}$, the estimate of the MTD (see Figure 3 for symbol definitions)

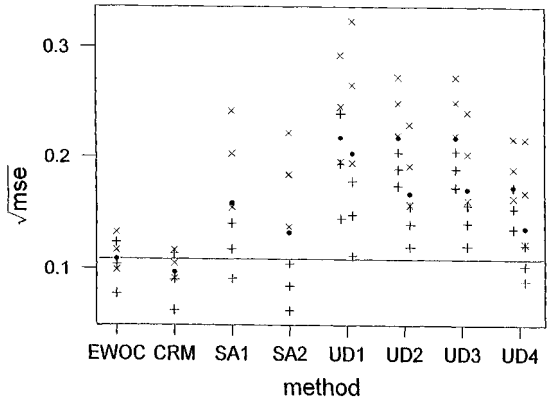

Figure 10. Average root mean squared error ($\sqrt{\text{MSE}}$) of $\hat{\gamma}$, the estimate of the MTD (see Figure 3 for symbol definitions)

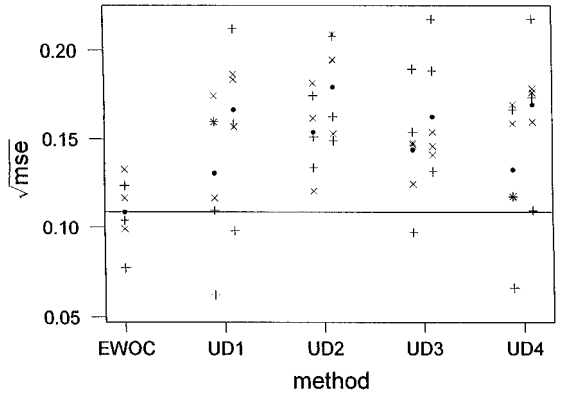

Figure 11. Average root mean squared error ($\sqrt{\text{MSE}}$) of $\hat{\gamma}$, the estimate of the MTD (see Figure 3 for symbol definitions)

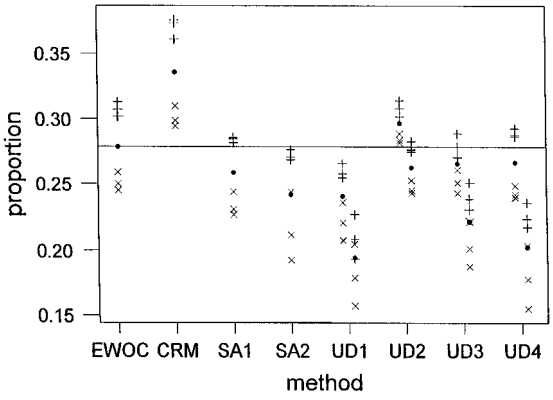

Figure 12. Proportion of patients exhibiting dose-limiting toxicity (see Figure 3 for symbol definitions)

Figure 12 shows the proportion of patients exibiting dose-limiting toxicity. For each of the six cases considered the proportion of DLTs observed for EWOC was less than that observed for CRM. Except for UD2, the overall production of DLTs observed for each of the non-parametric schemes was below that observed for EWOC and further from the target $\theta = 1/3$. In this sense, EWOC more closely approximated what would happen in the ideal situation where we treat all patients at the MTD. This might help explain why the non-parametric schemes estimated the MTD with significantly lower accuracy than EWOC, even when using the same estimator (Figures 9 and 11).

4. CONCLUDING REMARKS

In this paper, we describe a dose escalation scheme for cancer phase I clinical trials. It addresses the ethical demands that underlie cancer phase I trials by selecting doses so that the predicted proportion of patients who received an overdose is no greater than a specified value α. In simulation studies, the overall proportion of patients overdosed by EWOC was less than α. Hence, we observed that EWOC is an effective means of controlling the frequency of overdosing in a phase I clinical trial.

Relative to CRM, EWOC overdosed a smaller proportion of patients, exhibited fewer dose-limiting toxicities and estimated the MTD with slightly lower average bias and marginally higher mean squared error. Consequently, while the Bayesian schemes were comparable with respect to the accuracy with which they estimated the MTD, the frequency and degree of overdosing was significantly lower for EWOC.

Relative to the non-parametric dose escalation schemes, EWOC treated fewer patients at dose levels that were either subtherapeutic or severely toxic, treated a higher proportion of patients at doses near the MTD and estimated the MTD with lower average bias and mean squared error. We conclude that EWOC is a potentially useful alternative to currently implemented phase I designs. Further study is needed to determine how EWOC compares to competing dose escalation schemes under more general circumstances, how robust it is to the choice of prior PDF and mispecification of the model for the dose–toxicity relationship and how it performs when the trial is based on a small number of preselected dose levels. Ultimately, to assess adequately

EWOC's utility it is necessary to evaluate its performance in actual cancer phase I clinical trials. To date, EWOC has been used to design twelve phase I studies approved by the Research Review Committee and the Institute Review Board of the Fox Chase Cancer Center.

In nearly all practical applications, the posterior cumulative distribution function, π_k, of the MTD will be continuous and strictly increasing. The EWOC dose x_k given by (5) is then unique and can be computed by using a numerical root-finding algorithm such as bisection to approximate the root of $\alpha - \pi_k(x) = 0$ in the interval $[X_{\min}, X_{\max}]$. (Interested readers may obtain software to perform the necessary computations by correspondence with the authors.) In a more general setting, there may not exist a unique zero of $\alpha - \pi_k(x)$ in the allowed dose range. We then select for the kth patient the dose

$$x_k = \max\{x \in [X_{\min}, X_{\max}] : \pi_k(x) \leqslant \alpha\}.$$

We note that the dose sequence defined above is optimal Bayesian-feasible under all circumstances.

In its present formulation EWOC presupposes knowledge of dose levels $X_{\min}$ and $X_{\max}$ which bracket the MTD. This assumption can be removed by choosing a marginal prior distribution for the MTD that is positive on $(0, \infty)$ (for example, a normal distribution with positive mean truncated at zero). Alternatively, the trial can be conducted in stages with adjustments made to the allowed dose range after each stage. These modifications are currently under investigation.

To address best the needs of each individual patient, a dose escalation scheme should incorporate relevant patient information such as Karnofsky status and disease stage. Furthermore, phase I trials typically provide more information about toxicity than EWOC uses. Specifically, EWOC is based on a single binary response variable whereas toxicity is typically measured on a multinomial scale (graded according to National Cancer Institute toxicity criteria) and several distinct types of toxicity may be possible. Consequently, there are studies underway to extend EWOC to accommodate patient covariates and to utilize more informative multinomial and multivariate response measures.

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