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Use of a failure probability constraint to suggest an initial dose in a phase I cancer clinical trial

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ABSTRACT

The primary objective of a Phase I cancer clinical trial is to determine the maximum tolerated dose of a drug. The "failure probability" was proposed and used as a constraint to help identify a suitable initial dose range. The maximum tolerated dose was then determined based on a 3 + 3 cohort-based escalation scheme. Multiple simulations were conducted, and the method was evaluated according to the required sample size and accuracy and precision of maximum tolerated dose estimate. The results indicated that the median of the initial dose range suggested using a failure probability is a suitable initial dose regardless of the dose escalation sequence used for a cancer Phase I study. This initial dose required a smaller sample size and resulted in less bias of the estimated maximum tolerated dose compared with a commonly used initial dose, that is, 10% of the lethal dose. We tested our approach using real dose and toxicity outcome data from two published Phase I studies. These results indicate that adding a failure probability constraint into the calculation of the initial dose range will improve the efficiency of Phase I cancer trials.

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1. Introduction

A Phase I cancer clinical trial is conducted to determine the maximum tolerated dose (MTD) of a drug, which is the highest dose at which only a predefined, acceptable proportion of participants experience dose-limiting toxicity (DLT) [1,2].

The MTD is determined using a dose escalation scheme. Two types of escalation schemes are commonly used: cohort-based [3,4] and model-based [5,6] schemes. The 3 + 3 cohort-based scheme (3 + 3 design) is widely used owing to its simple method of calculating the numbers of participants who experience DLT. This design starts with a cohort of three participants. If no DLT occurs in this cohort, another three participants are recruited and given the drug at a higher dose. If one DLT occurs, three more participants are recruited at the same dose level. The dose escalation proceeds until at least two DLTs occur at a given dose. In the 3 + 3 design, the MTD is the maximum dose at which less than 33% of participants experience DLT [7,8].

Common dose escalation sequences are (i) the Fibonacci sequence (FS), in which each dose is the sum of the two previous doses [9]; (ii) the smoothed modified Fibonacci sequence (SMFS), which is similar to the FS but with a modification, relative increments are 100%, 67%, 50%, 40%, and 33% thereafter, to avoid DLT with subsequent higher doses [10,11]; (iii) the golden ratio increment sequence (GRIS), which is a 61.8% increment in each dose, the percentage obtained from the convergence of the FS [12]; and (iv) the multiple constant dose increment sequence (MCDIS), in which the dose escalates by a constant amount, usually a multiple of the initial dose [12–15].

The initial dose in a Phase I trial is usually determined from preclinical animal studies and is calculated based on 10% of lethal dose (LD_{10}) in rodents, one-sixth of the highest non-severely toxic dose in non-rodents, or no observed adverse effect levels in tested animals and body surface area [16–18]. Too low an initial dose is unsatisfactory because it may yield a low number of DLTs and require a large number of participants to determine the MTD. Too high an initial dose is also unsatisfactory because it may yield too many DLTs and fail to find the MTD. Thus, choosing the correct initial dose is of the utmost importance in a Phase I clinical trial.

The use of probability functions to calculate the likelihood of DLT as a function of dose has been proposed in a model-based approach [5]. Even if the unknown toxicity function can be arbitrarily assigned, the appropriate parameters in the function can only be solved with additional information; once the parameters have been estimated, however, MTD can be estimated. Theoretically, if a 3 + 3 design is used, the MTD is the dose at which the probability of DLT is less than but close to 0.33. However, a review of published Phase I trials with a 3 + 3 design reported that the probability of DLT at MTD was between 0.17 and 0.26 [19]. The aim of this study was that an initial dose should be suggested to correspond to a more accurate DLT function and its dose escalation sequence.

The initial dose should be selected with caution and with particular consideration given to obtaining the appropriate MTD. Here we propose an approach that uses failure probability (FP) as a constraint to help choose the initial dose. We hypothesize that use of FP to suggest initial dose would reduce the bias associated with the MTD and reduce the required sample size to determine MTD.

2. Methods

2.1. Dose-limiting toxicity probability function

Non-decreasing functions such as hyperbolic tangent functions, probit functions, and logit functions have been used to represent the relation between dose and toxicity [5,6,20]. Among them, the logit function is most common owing to its flexibility. The logit function is presented in Equation (1):

$$P(\mathrm{DLT}|\mathrm{Dose}=d_j)=p_j=\frac{e^{\alpha+\beta d_j}}{1+e^{\alpha+\beta d_j}},\ \infty>\alpha>-\infty,\beta>0, \tag{1}$$

where d_j denotes the j^{th} dose corresponding to the specific initial dose and $j = 1, 2, \ldots, J$, and α and β are unknowns that can be estimated. We constrained parameter α in the logit function to be greater than a constant in order to ensure a positive DLT probability when the dose is zero. We then estimated β with d_1, where d_1 is obtained based on LD_{10}. DLT probability at d_1 is 0.01. If DLT probability is overestimated, then the MTD estimate will be conservative. Thus, values of β are critical to the outcome of the logit function.

2.2. Failure probability

FP can be regarded as the expected probability of a particular dose being the MTD if the initial dose was selected appropriately. It is defined as the probability that MTD fails to be determined given J dose levels with a particular initial dose, d_1, as shown in Equation (2):

$$\mathrm{FP}=P(MTD<d_1)+P(MTD\geq d_J)=T^{(1)}+\prod_{j=1}^{J}\left(1-T^{(j)}\right), \tag{2}$$

where $T^{(j)}$ is the probability of stopping the escalation at d_j. Lin and Shih [4] calculated $T^{(j)}$ from $Bin(3, p_j)$ in a 3 + 3 design, which is simply a cumulative probability from the binomial distribution.

We defined $P(MTD = d_j)$ as the conditional probability that d_j is the MTD, as presented in Equation (3):

$$\begin{aligned}&P(MTD=d_j)\\&=P\frac{(\text{escalation at dose level}\leq d_j;\text{stop escalation at dose level } d_{j+1})}{P(\text{MTD is determined})}\\&=\frac{T^{(j+1)}\prod_{t=1}^{j}\left(1-T^{(t)}\right)}{1-\left(T^{(1)}+\prod_{t=1}^{J}\left(1-T^{(t)}\right)\right)},j=1,\ldots,J-1.\end{aligned} \tag{3}$$

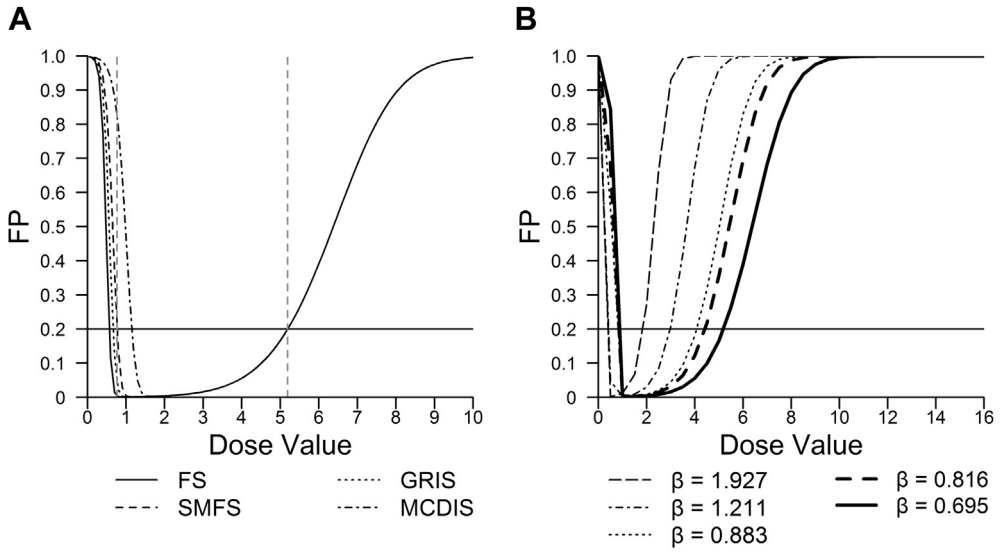

Fig. 1 – Failure probability (FP). (A) FP versus dose for each of the four dose escalation sequences calculated using a logit DLT function with $\alpha = -5.3$ and $\beta = 0.695$. The horizontal line represents 20% FP. The range indicated by the two vertical dashed lines represents the suggested initial dose range for SMFS. (B) FP versus dose calculated using a logit DLT function with $\alpha = -5.3$ and various values of β. Horizontal line represents 20% FP. DLT = dose-limiting toxicity; SMFS = smoothed modified Fibonacci sequence.

Consideration of FP increasing the confidence in MTD is successfully determined before the start of the trial. A range of suitable initial doses can be determined by solving the inequality equation that FP is less than a certain threshold.

2.3. *Sample size*

The expected sample size required at each dose level was derived by Lin and Shih [4], and we extended this calculation to determine the expected sample size required for the whole trial (N) as shown in Equation (4):

$$E(N) = \sum_{j=1}^{J-1}\left[E\left(n_j \middle| MTD = d_j\right)P\left(MTD = d_j\right)\right]$$

$$= \sum_{j=1}^{J-1}\left\{\left[3(j+1)3\sum_{k=1}^{j}\left(\frac{U^{(k)} - T^{(k)}}{1 - T^{(k)}}\right) + 3\frac{U^{(j+1)}}{T^{(j+1)}}\frac{U^{(j+1)} - T^{(j+1)}}{1 - U^{(j+1)}}\right]\frac{T^{(j+1)}\prod_{k=1}^{j}\left(1 - T^{(k)}\right)}{1 - T^{(1)} - \prod_{j=1}^{J}\left(1 - T^{(j)}\right)}\right\}, \quad (4)$$

where $E(n_j|MTD = d_j)$ is the expected sample size with d_j is the MTD, and $U^{(j)} = 1 - \binom{3}{0}p_j^0(1-p_j)^3$ is the probability that at least one DLT occurred at d_j ($j = 1, 2, \ldots, J-1$).

2.4. *Simulation studies*

Simulations were carried out using R version 2.15.1 (The R Foundation for Statistical Computing, Vienna, Austria). We used 20% as the FP constraint to determine the initial dose range and select the initial dose for use in simulations. DLT probability for each dose escalation sequence (FS, SMFS, GRIS, or MCDIS) was generated from the assumed true probability using the logit function with random deviation ε_j. DLT probability was represented as shown in Equation (5):

$$P\left(DLT|Dose = d_j\right) = \frac{e^{\alpha+\beta d_j+\varepsilon_j}}{1 + e^{\alpha+\beta d_j+\varepsilon_j}}, \quad (5)$$

where $\varepsilon_j^{iid} \sim N(0, \sigma^2)$ and σ^2 represents the variability in reception to the toxic response of the drug for an individual at d_j.

Parameters $\alpha = -5.3$ and $\beta = 1.927$, 1.211, 0.883, 0.816, and 0.695 were used to ensure low DLT probability at dose zero and a smooth, increasing trend of the logit function. Simulations were performed with σ^2 ranging from 0.2 to 2.0 in increments of 0.2.

The probability of DLT occurrence was generated from *Uniform*(0, 1). A DLT was regarded to have occurred if the generated probability was smaller than the true DLT probability, which was generated from Equation (5). The 3 + 3 design was followed to determine whether the dose should be raised

to a higher level. Simulations were iterated until MTD had been successfully estimated 1000 times for each initial dose. Simulated expected overall sample size, average number of DLTs, average MTD estimate, and accuracy of MTD estimate (i.e., percentage bias) were obtained. Percentage bias is a common metric in evaluating the simulation [21] and was defined as $(\overline{\hat{d}}_{MTD} - d_{MTD})/d_{MTD} \times 100\%$, where $\overline{\hat{d}}_{MTD}$ is the estimate of MTD, $\overline{\hat{d}}_{MTD} = 1/1000 \sum_{i=1}^{1000} \hat{d}_{MTD,i}$, and d_{MTD} is the true MTD. Theoretically, d_{MTD} can be solved in the DLT functions and used as a reference value for simulation.

Data from two published studies were used to compare the proposed method to real data.

3. Results

3.1. Simulation studies

The initial dose ranges obtained for each dose escalation sequence are displayed in Fig. 1A. The initial dose range was obtained by drawing a horizontal line at 20% of FP. The FP values calculated for the SMFS dose escalation sequence with different initial doses using different scale parameters in the logit DLT function are displayed in Fig. 1B. The initial dose range became smaller as β increased for the same dose escalation sequence. The initial dose range is shown in Fig. 2.

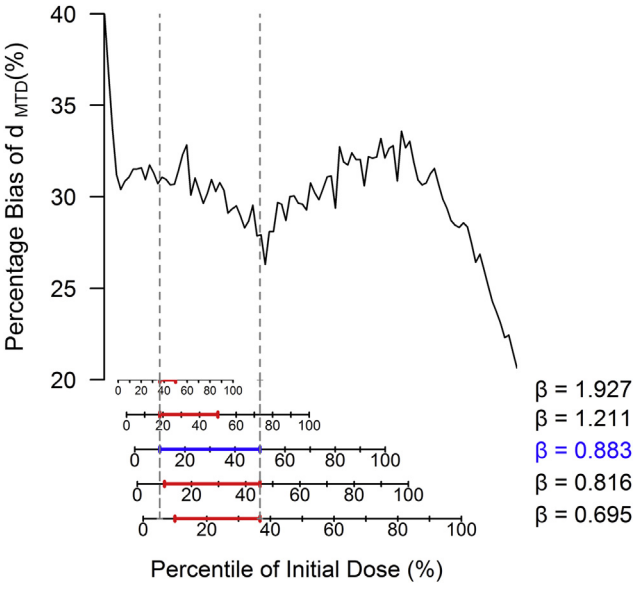

Fig. 2 – True percentage bias with different initial dose ranges. The percentage bias calculated from the true DLT function with $\alpha = -5.3$ and $\beta = 0.883$. The x axis is the percentile of the derived initial dose range that was used as the initial dose. The blue bar represents the initial dose suggested by the true DLT function. The percentage bias was similar between the 10th and 50th percentiles of the derived initial dose range. If the wrong DLT function (e.g., the same α value and β = 0.695, 0.816, 1.211, 1.927) was used to estimate initial dose, the suggested initial dose range would be represented by the red bar that overlaps the true initial dose range. The suggested initial dose was appropriate even if the estimate of β deviated from the true value of β because the difference in percentage bias between the 10th and 50th percentiles of the derived initial dose range was small and the suggested initial dose range overlapped the initial dose range that suggested from the true DLT function. DLT = dose-limiting toxicity.

The sample size, number of DLTs, percentage bias, and precision for each dose escalation sequence are displayed in figures for every 10th percentile increment of the initial dose range. Variables were calculated in this way because the absolute values of the initial dose ranges were not the same across the four dose escalation sequences and across different β values. Only the results obtained with $\alpha = -5.3$, $\beta = 0.695$, and $\sigma = 1.2$ are presented because other results were similar.

Fig. 3A shows the total sample size and number of DLTs in the simulated Phase I trial. These results indicated that 9.5 participants would be needed and DLT would be expected in 2.8 participants if SMFS was used and the 50th percentile (median) of the derived initial dose range was used as the initial dose. The required sample size decreased when the initial dose increased within the derived initial dose range. The results indicated that smaller sample sizes were needed when SMFS or MCDIS was used as the dose escalation sequence than when FS or GRIS was used as the dose escalation sequence. The average number of participants with DLT was approximately three in each simulation for all doses, as expected for a 3 + 3 design.

The percentage bias of MTD was always negative because estimates of MTD were always lower than the true MTD. For simplicity, the percentage bias was expressed with positive values in the simulation results. The percentage bias for all derived initial doses was between 15% and 40% for all dose escalation sequences (Fig. 3B). If the initial dose was between the 10th and 60th percentile of the derived initial dose range then the percentage bias was similar for all dose escalation sequences (Fig. 3B). If the initial dose was below the 10th percentile of the derived initial dose range, the percentage bias was greater (Fig. 3B). GRIS yielded a smaller percentage bias when the initial dose was above the median of the derived initial dose range. In all four dose escalation sequences, the smallest percentage bias occurred when the initial dose was above the 90th percentile of the derived initial dose range.

Precision was defined as the number of successful simulations (i.e., simulations that achieved the goal of establishing an MTD) divided by the total number of runs in the simulation. Higher precision represents a higher probability that the initial dose chosen in that particular sequence would eventually establish an MTD. Precision was greater than 95% if the initial dose was between the 10th and 50th percentile of the derived initial dose range (Fig. 3C).

When taking all four metrics into considerations, results of simulation with an FP constraint suggested that the initial dose should be between the 10th and 50th percentile of the derived initial dose range for all four dose escalation sequences.

We performed simulations in which we considered various values of β in the logit function and showed that the calculated initial dose range changed smoothly with β. The suggested initial doses (10th to 50th percentile of the derived

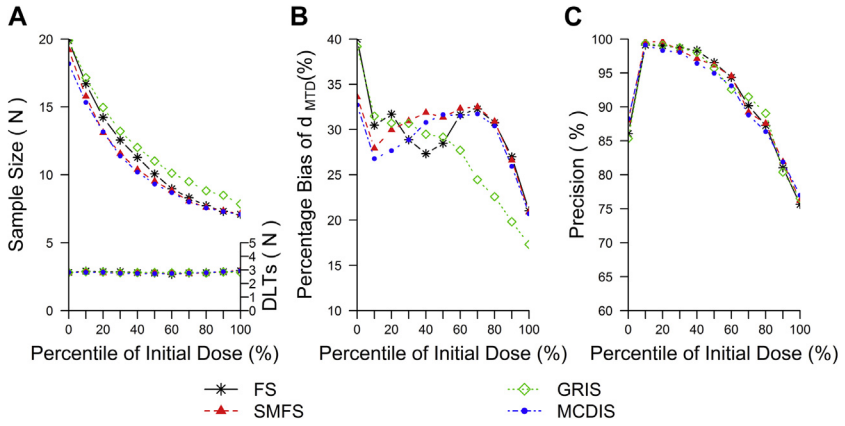

Fig. 3 – Sample size, number of DLTs, and bias and precision of MTD estimate versus percentile of the initial dose range. (A) Sample size and number of DLTs, (B) percentage bias, and (C) precision of the MTD estimate calculated using a logit DLT function with $\alpha = -5.3$ and $\beta = 0.695$ for each for the four dose escalation sequences. The individual deviation of DLT probability was distributed as N(0, 1.44). The x axis is the percentile of the derived initial dose range that was used as the initial dose. The left y axis in (A) represents the sample size used in the escalation process, and the right y axis in (A) represents the number of DLTs that occurred in the escalation process. DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

initial dose range) were greatly overlapped when the range was calculated with different values of β. Most importantly, the simulation demonstrated that the total sample size, number of DLTs, and percentage bias were similar across different values of β when the median of the initial dose range was selected as the initial dose. The metrics derived from the simulation provide strong evidence for this (Fig. 4).

Fig. 5 demonstrates that the relation among variability (σ) and sample size, number of DLTs, and percentage bias was similar for all four dose escalation sequences. The required sample sizes were similar for all assumed values of σ. However, the percentage bias of the estimated MTD increased with variability. These findings were the same for all four dose escalation sequences.

3.2. *Comparison with published data*

The sample size and number of DLTs obtained with the proposed simulation method were compared with two published Phase I cancer trials: the use of holmium-166 radioembolization (^{166}Ho-radioembolization) for patients with unresectable, chemorefractory liver metastases [14] and the use of vandetanib for patients with recurrent malignant gliomas [15]. Both studies had a 3 + 3 design with an MCDIS dose escalation sequence.

The ^{166}Ho-radioembolization study used 20 Gy as the initial dose and found 60 Gy to be the MTD. The total sample size was 15, and there were three DLTs [14]. Using the proposed approach with FP = 20% and MCDIS, the derived values of α

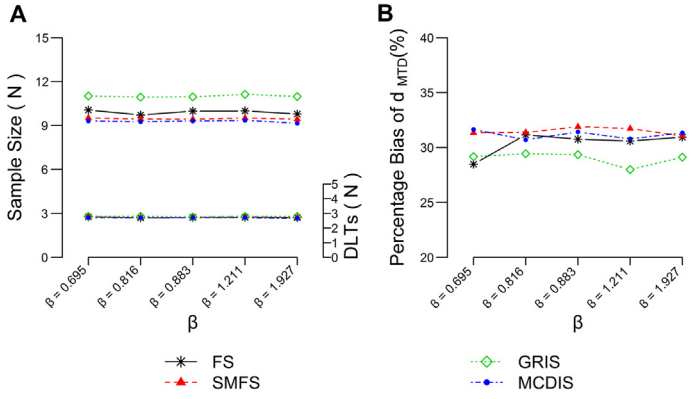

Fig. 4 – Sample size, number of DLTs, and accuracy of $\widehat{d}_{MTD}$ with different β values. A logit DLT function with $\alpha = -5.3$ and different β values was used for all dose escalation sequences. The median of the derived initial dose range was used as the initial dose, and the individual deviation of the DLT probability was distributed as N(0, 1.44). The left y axis in (A) represents the sample size used in the escalation process, and the right y axis in (A) represents the number of DLTs that occurred in the escalation process. DLT = dose-limiting toxicity.

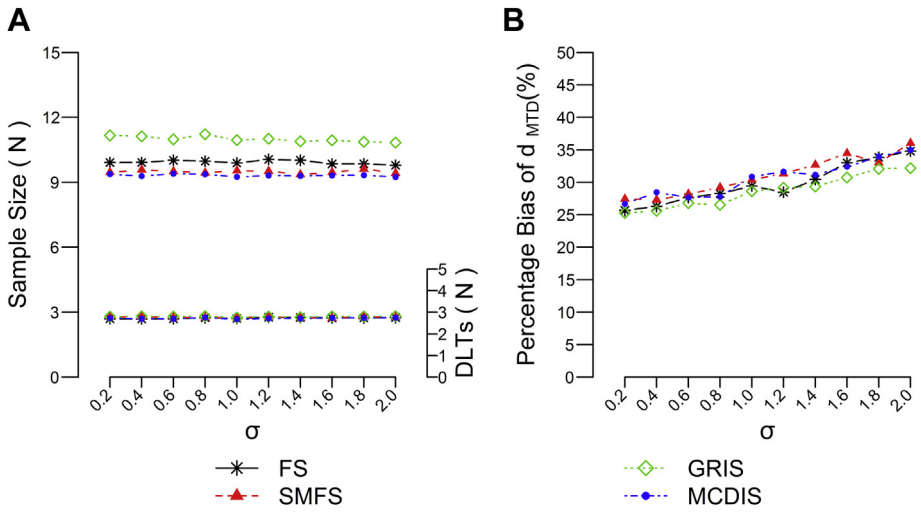

Fig. 5 – Sample size, number of DLTs, and accuracy of $\bar{\hat{d}}_{MTD}$ with different σ values. A logit DLT function with $\alpha = -5.3$ and $\beta = 0.695$ and different individual σ values was used for all dose escalation sequences. The median of the derived initial dose range was used as the initial dose. The left y axis in (A) represents the sample size used in the escalation process, and the right y axis in (A) represents the number of DLTs that occurred in the escalation process. DLT = dose-limiting toxicity.

and β were −5.29 and 0.07, and the initial dose range was 11.43–51.53 Gy. If the median of this range (30 Gy) was used as the initial dose, our method predicted an MTD of 60 Gy with a required sample size of 9.7 and 2.8 DLTs.

The vandetanib study used 100 mg as the initial dose and found 100 mg to be the MTD. The total sample size was 10, and there were three DLTs [15]. Using the proposed approach with FP = 20% and MCDIS, the derived values of α and β were −5.29 and 0.024, and the initial dose range was 33.33–150.32 mg. If the median of this range (90 mg) was used as the initial dose, our method predicted an MTD of 180 mg with a required sample size of 9.3 and 2.7 DLTs. Some other studies confirmed that the dose can be tolerated as high as 300 mg [22,23].

4. Discussion

This study proposed and used an FP constraint and performed several simulations to determine MTD using four different dose escalation sequences. The results suggested that the proposed method could be helpful for determining MTD with a smaller sample size and less bias.

This study used a logit function to model the relation between dose and toxicity. The scale parameter β in the logit function was estimated using a dose derived from animal studies. The value of β is critical to the study because it greatly affects the shape of the logit function and thus affects DLT probability at each dose level. β represents the degree of instantaneous increment in DLT probability. Mathematically, it is inversely related to the size of the initial dose range. The dose ranges calculated with different values of β overlapped (Fig. 2), and the dose range from one particular β estimate was largely covered by other β estimates with the same dose escalation sequence, suggesting that the initial dose estimate may be appropriate even when the estimate of β deviates from its true value.

Notably, with FS, SMFS, and MCDIS, the bias decreased to 20% when the initial dose was between the 70th and 100th percentile of the initial dose range (Fig. 3B). With each dose escalation, the second dose is twice as large as the initial dose. Each initial dose is MTD if the DLT probability of the initial dose is lower than the target DLT probability and the DLT probability of the second dose is higher than the target DLT probability. In this situation, the bias decreases as initial dose increases. Although the MTD will have smaller bias and require a smaller sample size, the precision of the simulation with such initial doses will become much lower, reducing the chances of successfully determining MTD.

In our method, the dose increment in MCDIS was dependent on the initial dose. Some studies have used a constant dose increment but different magnitude of initial dose [24,25], and other studies have increased the dose with irregular increments [26,27]. In practice, the dose increments should be determined according to the pharmacological characteristics of the drug. However, the relative increase of subsequent dose increments will not change or will decrease for all four dose escalation sequences.

There are a few limitations to this study. First, the proposed method heavily relies on toxicity information from animal studies, that is, LD_{10}. Toxicity information from animal studies is limited and can sometimes be confidential as it is acquired in the early stages of drug development. Thus, one should be cautious when estimating α and β in the logit function. Second, we only considered a logit DLT function. Although this is the most widely used function, other functions can be used such as a hyperbolic tangent function. Third, all MTD estimates heavily depend on the escalation scheme. The 3 + 3 design is one of the most common schemes in use and is a special case of the A + B design [4], but our proposed

method can also be extended to other, more complicated schemes.

Our proposal of adding an FP constraint into the suggestion of the initial dose will help the design of Phase I cancer trials, making them more efficient and more economical. In general, our study suggests that the median of the derived initial dose range should be chosen as the initial dose of a Phase I study regardless of the dose escalation sequence used.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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