

Statistical Properties of The Traditional Algorithm-based Designs for Phase I Cancer Clinical Trials

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SUMMARY

Although there are several new designs for phase I cancer clinical trials including the continual reassessment method and accelerated titration design, the traditional algorithm-based designs, like the ‘3+3’ design, are still widely used in practice because of their simplicity for clinical investigators to carry out the experiment. In this paper, we study some key statistical properties of the traditional algorithm-based designs in a general framework and derive the exact formulas for the corresponding statistical quantities. These quantities are important for the investigator to gain insights regarding the design of the trial, which are: (i) Probability of a dose being chosen as the MTD (maximum-tolerated dose); (ii) Expected number of patients treated at each dose level; (iii) Target toxicity level (i.e., the expected DLT, dose-limiting toxicity, incidences at the MTD); (iv) Expected DLT incidences at each dose level; (v) Expected overall DLT incidences in the trial. Real examples of clinical trials are given, and a computer program to do the calculation can be found in authors’ website.

Some key words: Algorithm-based design; Phase I cancer clinical trial; MTD.

1. INTRODUCTION

The main goals of a phase I cancer clinical trial are to find the maximum tolerated dose (MTD) of a drug for a specific mode of administration and to characterize the most frequent and dose-limiting toxicities (DLT)[Carter 1987]. The highest possible dose is sought, since the benefit of the new treatment is believed to increase with dose. The MTD is often defined as the highest dose level at which, say, 20, 33, or 50 per cent of patients experience DLT. The recommended phase II dose level is usually either the MTD or one dose level below the MTD [Dent and Eisenhauer 1996].

Prior to the enrollment of patients in a trial, the notion of dose limiting toxicity is specifically defined. Usually in the United States, the NCI (National Cancer Institute) Common Toxicity Criteria is used. The DLT is defined as a group of toxicities of grade three or higher, depending on the haematologic and non-haematologic toxicities, where the grades are defined as follows: grade 0, no toxicity; grade 1, mild toxicity; grade 2, moderate toxicity; grade 3, severe toxicity; grade 4, life-threatening toxicity.

The traditional phase I cancer clinical trials use two-stage algorithm-based designs. The designs begin with the selection of a starting dose based on animal studies, usually one-tenth of the lethal dose in mice or one-third toxic low dose in dogs, or based on the information from individual drugs if a combination of several drugs that have toxicity information are used in the trial. The dose level usually follows a modified Fibonacci scheme, such as the dose sequence 1.0, 2.0, 3.3, 5.0, 7.0, 9.0, 12.0, 16.0 (dose increments of 100%, 65%, 52%, 40%, 29%, 33%, 33%), with early doses based on large dose increments which get smaller for higher doses [Edler 1990]. Three or six patients are treated at each dose level, depending on the observed toxicity until a specified number of DLT incidences is observed at a dose level. The details of the design in a general framework will be discussed in Section 3.

Despite the fact that the traditional method for dose escalation has been criticized for its tendency to include too many patients at suboptimal dose levels and give a poor estimate of the MTD [O'Quigley *et al.* 1990, Heyd and Carlin 1999], it is still widely used in practice because of its algorithm-based simplicity in logistics for the clinical investigators to carry out, compared to, say, the various model-based CRMs (continual reassessment methods) [O'Quigley *et al.* 1990, Heyd and Carlin 1999].

It is perhaps somewhat surprising that the statistical properties of the traditional algorithm-based designs, although commonly used, are not systematically studied in the literature. Many have used limited computer simulations to demonstrate certain particular points in comparison with other methods [Korn *et al.* 1994, Smith *et al.* 1996]. In this paper, our purpose is not to compare methods; rather, we study some key statistical properties of the traditional algorithm-based designs in a general framework and derive the exact formulas for the corresponding statistical quantities. These quantities are: (i) The probability of a dose being chosen as MTD; (ii) The expected number of patients at each dose level; (iii) The target toxicity level (TTL, i.e., the expected DLT incidences at MTD); (iv) The expected DLT incidences at each dose level; (v) The expected overall DLT incidences in the trial. It has been our experience that showing these quantities really helps the clinical investigator to grasp the properties of a given trial design before the trial starts.

All the statistical properties discussed in this paper are based on the toxicity rate at each dose level selected for the trial. Of course the exact dose-toxicity curve is not known in advance, but the clinicians should have some knowledge, no matter how weak that knowledge may be, of the drug toxicity based on similar trials or other source of information. (Otherwise, it would be very difficult for the investigator to justify the dose levels selected for testing.) Several different scenarios, including the best and worst possible cases, may be considered back and forth during

the design stage to gain insights on the trial design.

2. NOTATION AND CONVENTION

Let A , B , C , D , and E be integers. We use the notation A/B to mean A toxicity incidences out of B patients and $> A/B$ to mean more than A toxicity incidences out of B patients. Similarly the notation $A/B + \leq C/D$ means that A toxicity incidences in the first cohort of B patients and no more than C toxicity incidences in the second cohort or both cohorts of D patients (depending on the specific design). We will also follow the convention that if the lower bound is greater than the upper bound in a summation or product sign, the corresponding summation or product term will not be included in the formula or equation. For example, $\sum_{i=2}^1 a(i)$ or $\prod_{i=1}^0 b(i)$ will be deleted.

In the following, we assume that there are n predefined dose with increasing levels and let p_i be the probability of observing DLT at dose level i for $1 \leq i \leq n$.

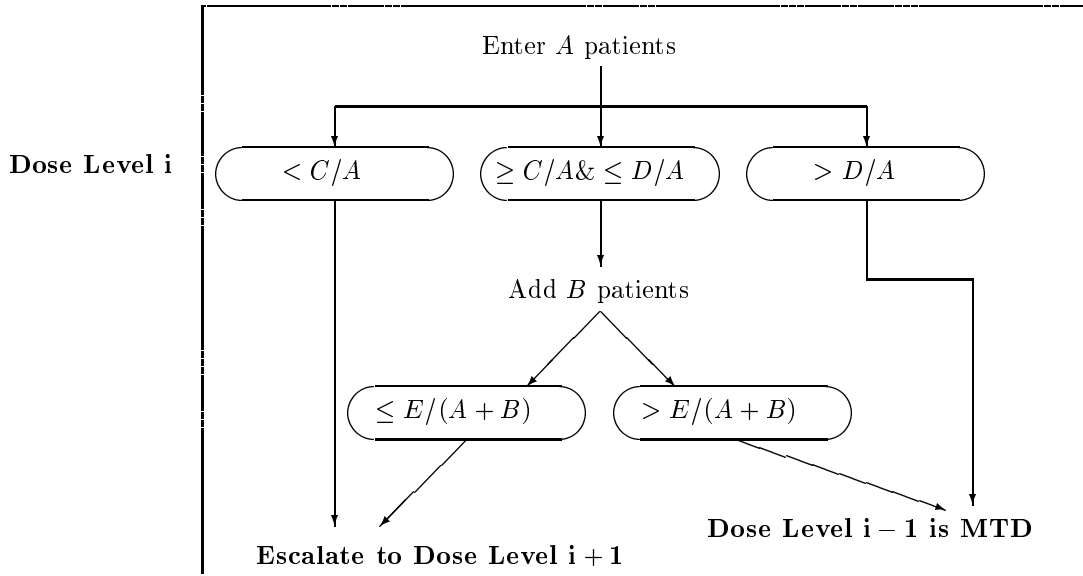
3. ALGORITHM-BASED DESIGNS

For the algorithm-based designs described in this section, if dose escalation is still indicated at the last (i.e., the highest) dose level n , then the MTD is at or above the last dose level. If the trial stops at the first dose, then the MTD is below the first dose level. In either of these two cases, the MTD is not determined from the trial.

3.1. General $A + B$ design without dose de-escalation

The general $A + B$ designs without dose de-escalation can be described as follows. Groups of A patients will be entered at a dose level i . If $< C/A$ patients have DLT, then the dose will be escalated to the next dose level $i + 1$. If $> D/A$ (where $D \geq C$) patients have DLT, then

Fig. 1. Escalation Scheme for $A + B$ design without dose de-escalation



the previous dose $i - 1$ will be considered the MTD. If $\geq C/A$ but $\leq D/A$ patients have DLT, B more patients will be treated at this dose level i . If no more than E (where $E \geq D$) of the total of $A + B$ patients have DLT, then the dose will be escalated. If more than E of the total of $A + B$ patients have DLT, then the previous dose $i - 1$ will be considered the MTD. Hence this is generally called ‘ $A + B$ ’ design, for which the traditional ‘ $3 + 3$ ’ is a special case; see [Edler 1990]. A diagram for the design is shown in Figure 1 to assist the understanding.

The traditional $3 + 3$ design without dose de-escalation is a special case of the general $A + B$ design with $A = B = 3$ and $C = D = E = 1$.

3.2. General $A + B$ design with dose de-escalation

The general $A + B$ designs with dose de-escalation is basically similar to the previous design, but permits more patients to be treated at a lower dose (i.e., dose de-escalation) when excessive

DLT incidences occur at the current dose level. Contrasting Figure 2 to Figure 1, the dose de-escalation occurs when $> D/A$ (where $D \geq C$) or $> E/(A + B)$ patients have DLT at dose level i , then B more patients will be treated at dose level $i - 1$, provided that only A patients have been previously treated at this prior dose; if more than A patients have already been treated previously, then dose $i - 1$ is the MTD. Of course, the de-escalation may continue to dose level $i - 2$ and so on if necessary.

In summary, for this design, the MTD is the dose level at which $\leq E/(A + B)$ patients experience DLT, and $> D/A$ or $(\geq C/A \ \& \ \leq D/A) + > E/(A + B)$ patients treated with the next higher dose have DLT. Again, the traditional 3+3 design with dose de-escalation is a special case of the general $A + B$ design with $A = B = 3$ and $C = D = E = 1$.

4. PROBABILITY OF A DOSE BEING CHOSEN AS MTD

In this section, we find the probability of a dose being chosen as MTD. Both the general $A + B$ designs, with and without dose de-escalation, will be considered. Notice that for the algorithm-based design described in Section 3, the probability of the last dose n being chosen as MTD is always 0. For convenience, we will use the notation “MTD = dose n ” to mean “MTD \geq dose n ” occasionally.

4.1. General $A + B$ design without dose de-escalation

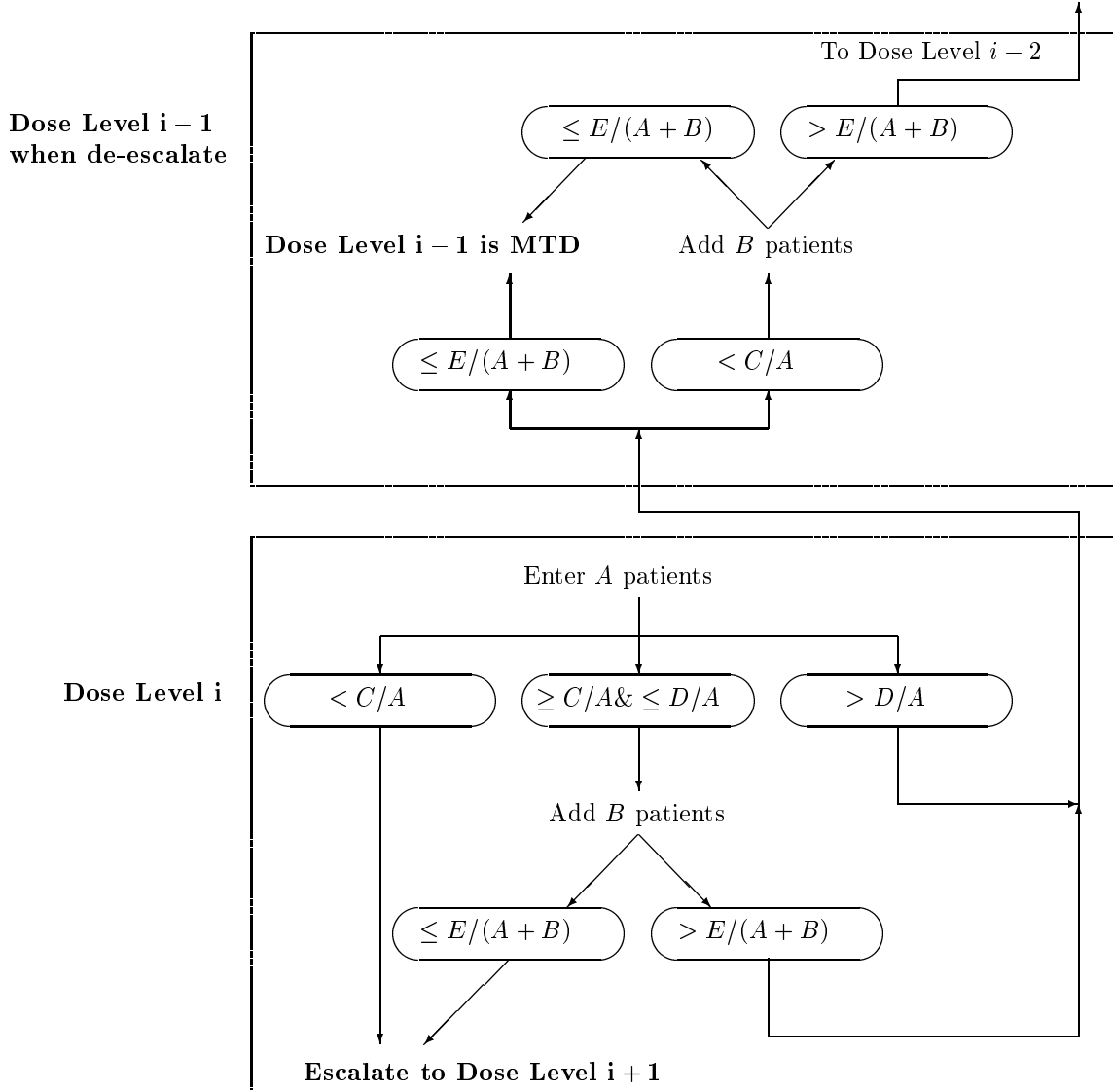
For $1 \leq j \leq n$, let

$$P_0^j = P(< C/A \text{ when treated at dose } j) = \sum_{k=0}^{C-1} \binom{A}{k} p_j^k (1 - p_j)^{A-k},$$

$$Q_0^j = P((\geq C/A \text{ but } \leq D/A) + \leq E/(A + B) \text{ when treated at dose } j)$$

$$= \sum_{k=C}^D \sum_{m=0}^{E-k} \binom{A}{k} p_j^k (1 - p_j)^{A-k} \binom{B}{m} p_j^m (1 - p_j)^{B-m}.$$

Fig. 2. Escalation Scheme for $A + B$ design with dose de-escalation



Then for $1 \leq i < n$,

$$P(\text{MTD} = \text{Dose } i) = P \left(\begin{array}{l} \text{escalation at dose } \leq i; \\ \text{stop escalation at dose } i + 1 \end{array} \right) = (1 - P_0^{i+1} - Q_0^{i+1}) \prod_{j=1}^i (P_0^j + Q_0^j),$$

$$P(\text{MTD} < \text{Dose } 1) = P(\text{stop escalation at dose } 1) = 1 - P_0^1 - Q_0^1,$$

and

$$P(\text{MTD} \geq \text{Dose } n) = P(\text{escalation at dose } 1 \leq j \leq n) = \prod_{j=1}^n (P_0^j + Q_0^j).$$

For the traditional 3+3 design without dose de-escalation, we have, for $1 \leq j \leq n$,

$$P_0^j = P(0/3 \text{ when treated at dose } j) = (1 - p_j)^3.$$

Let $P_1^j = P(1/3 \text{ when treated at dose } j) = 3p_j(1 - p_j)^2$, then $Q_0^j = P_1^j P_0^j$, so for $1 \leq i < n$,

$$P(\text{MTD} = \text{Dose } i) = \left(\prod_{j=1}^i (P_0^j + P_1^j P_0^j) \right) (1 - P_0^{i+1} - P_1^{i+1} P_0^{i+1}),$$

$$P(\text{MTD} < \text{Dose } 1) = 1 - P_0^1 - P_1^1 P_0^1 \quad \text{and} \quad P(\text{MTD} \geq \text{Dose } n) = \prod_{j=1}^n (P_0^j + P_1^j P_0^j).$$

4.2. General $A + B$ designs with dose de-escalation

For $1 \leq j \leq n$, let P_0^j and Q_0^j be defined as in section 4.1. In addition, let

$$P_1^j = P(\geq C/A \text{ but } \leq D/A \text{ when treated at dose } j) = \sum_{k=C}^D \binom{A}{k} p_j^k (1 - p_j)^{A-k},$$

$$\begin{aligned} Q_1^j &= P(< C/A + \leq E/(A + B) \text{ when treated at dose } j) \\ &= \sum_{k=0}^{C-1} \sum_{m=0}^{E-k} \binom{A}{k} p_j^k (1 - p_j)^{A-k} \binom{B}{m} p_j^m (1 - p_j)^{B-m}, \end{aligned}$$

and

$$\begin{aligned} Q_2^j &= P(< C/A + > E/(A + B) \text{ when treated at dose } j) \\ &= \sum_{k=0}^{C-1} \sum_{m=E+1-k}^B \binom{A}{k} p_j^k (1 - p_j)^{A-k} \binom{B}{m} p_j^m (1 - p_j)^{B-m}. \end{aligned}$$

Then for $1 \leq i < n$,

$$\begin{aligned}
P(\text{MTD} = \text{Dose } i) &= \sum_{k=i+1}^n P \left(\begin{array}{l} \text{escalation at dose } < i; \\ (\geq C/A \text{ but } \leq D/A) + \leq E/(A+B) \text{ or} \\ < C/A + \leq E/(A+B) \text{ at dose } i; \\ < C/A + > E/(A+B) \text{ at dose } i < j < k; \\ \text{stop escalation at dose } k \end{array} \right) \\
&= \sum_{k=i+1}^n \left(\prod_{j=1}^{i-1} (P_0^j + Q_0^j) \right) (Q_0^i + Q_1^i) \left(\prod_{j=i+1}^{k-1} Q_2^j \right) (1 - P_0^k - Q_0^k),
\end{aligned}$$

$$\begin{aligned}
P(\text{MTD} < \text{Dose } 1) &= \sum_{k=1}^n P \left(\begin{array}{l} < C/A + > E/(A+B) \text{ at dose } 1 \leq j < k; \\ \text{stop escalation at dose } k \end{array} \right) \\
&= \sum_{k=1}^n \left(\prod_{j=1}^{k-1} Q_2^j \right) (1 - P_0^k - Q_0^k),
\end{aligned}$$

and

$$P(\text{MTD} \geq \text{Dose } n) = P(\text{escalation at dose } 1 \leq j \leq n) = \prod_{j=1}^n (P_0^j + Q_0^j).$$

For the traditional 3 + 3 design with dose de-escalation, we have, for $1 \leq j < n$,

$$P_0^j = P(0/3 \text{ when treated at dose } j) = (1 - p_j)^3,$$

$$P_1^j = P(1/3 \text{ when treated at dose } j) = 3p_j(1 - p_j)^2,$$

$$Q_0^j = P_0^j P_1^j, Q_1^j = P_0^j (P_0^j + P_1^j) \text{ and } Q_2^j = P_0^j (1 - P_0^j - P_1^j),$$

so for $1 \leq i < n$,

$$\begin{aligned}
P(\text{MTD} = \text{Dose } i) &= \sum_{k=i+1}^n \left(\prod_{j=1}^{i-1} (P_0^j + P_1^j P_0^j) \right) (P_1^i P_0^i + P_0^i (P_0^i + P_1^i)) \times \\
&\quad \left(\prod_{j=i+1}^{k-1} (P_0^j (1 - P_0^j - P_1^j)) \right) (1 - P_0^k - P_1^k P_0^k),
\end{aligned}$$

$$P(\text{MTD} < \text{Dose } 1) = \sum_{k=1}^n \left(\prod_{j=1}^{k-1} (P_0^j (1 - P_0^j - P_1^j)) \right) (1 - P_0^k - P_1^k P_0^k)$$

and

$$P(\text{MTD} \geq \text{Dose } n) = \prod_{j=1}^n (P_0^j + P_1^j P_0^j).$$

5. EXPECTED NUMBER OF PATIENTS TREATED AT EACH DOSE LEVEL

In planning a clinical trial, it is important to know the number of patients needed in the trial. However, for a sequential design, it is not possible to know in advance the exact number of patients in the trial. But by knowing the probability of toxicity at each dose level, we can find the expected number of patients to be treated at each dose level, hence the expected number of patients in the trial.

In this section, let P_0^j, P_1^j and Q_0^j be defined as in Section 4.

5.1. General $A + B$ designs without dose de-escalation

For $1 \leq j \leq n$, let X_j be the number of patients to be treated at dose level j , then

$$E(X_j) = \sum_{i=0}^n E(X_j | \text{MTD} = \text{Dose } i) P(\text{MTD} = \text{Dose } i),$$

where

$$E(X_j | \text{MTD} = \text{Dose } i) = \begin{cases} \frac{AP_0^j + (A+B)Q_0^j}{P_0^j + Q_0^j} & \text{if } j \leq i \\ \frac{A(1-P_0^j - P_1^j) + (A+B)(P_1^j - Q_0^j)}{1 - P_0^j - Q_0^j} & \text{if } j = i + 1 \\ 0 & \text{if } j > i + 1. \end{cases}$$

For the traditional 3+3 design without dose de-escalation, we have

$$E(X_j | \text{MTD} = \text{Dose } i) = \begin{cases} \frac{3P_0^j + 6P_1^j P_0^j}{P_0^j + P_1^j P_0^j} & \text{if } j \leq i \\ \frac{3(1-P_0^j - P_1^j) + 6(P_1^j - P_1^j P_0^j)}{1 - P_0^j - P_1^j P_0^j} & \text{if } j = i + 1 \\ 0 & \text{if } j > i + 1. \end{cases}$$

5.2. General A + B designs with dose de-escalation

With dose de-escalation the formulas are more complicated. For $1 \leq j \leq n$,

$$\begin{aligned}
E(X_j) &= \sum_{i=0}^n E(X_j | \text{MTD} = \text{Dose } i) P(\text{MTD} = \text{Dose } i) \\
&= \sum_{i=0}^{n-1} \sum_{k=i+1}^n E \left(X_j \left| \begin{array}{l} \text{MTD} = \text{Dose } i \text{ and} \\ \text{stop escalation at dose } k \end{array} \right. \right) \times \\
&\quad P(\text{stop escalation at dose } k | \text{MTD} = \text{Dose } i) P(\text{MTD} = \text{Dose } i) \\
&\quad + E(X_j | \text{MTD} = \text{Dose } n) P(\text{MTD} = \text{Dose } n) \\
&= \sum_{i=0}^{n-1} \sum_{k=i+1}^n E \left(X_j \left| \begin{array}{l} \text{MTD} = \text{Dose } i \text{ and} \\ \text{stop escalation at dose } k \end{array} \right. \right) P \left(\begin{array}{l} \text{MTD} = \text{Dose } i \text{ and} \\ \text{stop escalation at dose } k \end{array} \right) \\
&\quad + E(X_j | \text{MTD} = \text{Dose } n) P(\text{MTD} = \text{Dose } n),
\end{aligned}$$

where

$$E \left(X_j \left| \begin{array}{l} \text{MTD} = \text{Dose } i \text{ and} \\ \text{stop escalation at dose } k \end{array} \right. \right) = \begin{cases} \frac{AP_0^j + (A+B)Q_0^j}{P_0^j + Q_0^j} & \text{if } j < i \\ A + B & \text{if } i \leq j < k \\ \frac{A(1-P_0^j - P_1^j) + (A+B)(P_1^j - Q_0^j)}{1 - P_0^j - Q_0^j} & \text{if } j = k \\ 0 & \text{if } j > k, \end{cases}$$

$$E(X_j | \text{MTD} = \text{Dose } n) = \frac{AP_0^j + (A+B)Q_0^j}{P_0^j + Q_0^j},$$

and

$$P \left(\begin{array}{l} \text{MTD} = \text{Dose } i \text{ and} \\ \text{stop escalation at dose } k \end{array} \right) = \left(\prod_{j=1}^{i-1} (P_0^j + Q_0^j) \right) (Q_0^i + Q_1^i) \left(\prod_{j=i+1}^{k-1} Q_2^j \right) (1 - P_0^k - Q_0^k).$$

For the traditional 3+3 design with dose de-escalation, we have

$$E \left(X_j \middle| \begin{array}{l} \text{MTD} = \text{Dose } i \text{ and} \\ \text{stop escalation at dose } k \end{array} \right) = \begin{cases} \frac{3P_0^j + 6P_1^j P_0^j}{P_0^j + P_1^j P_0^j} & \text{if } j < i \\ 6 & \text{if } i \leq j < k \\ \frac{3(1 - P_0^j - P_1^j) + 6(P_1^j - P_1^j P_0^j)}{1 - P_0^j - P_1^j P_0^j} & \text{if } j = k \\ 0 & \text{if } j > k, \end{cases}$$

$$E(X_j | \text{MTD} = \text{Dose } n) = \frac{3P_0^j + 6P_1^j P_0^j}{P_0^j + P_1^j P_0^j},$$

and

$$P \left(\begin{array}{l} \text{MTD} = \text{Dose } i \text{ and} \\ \text{stop escalation at dose } k \end{array} \right) = \left(\prod_{j=1}^{i-1} (P_0^j + P_1^j P_0^j) \right) (P_1^i P_0^i + P_0^i (P_0^i + P_1^i)) \times \\ \left(\prod_{j=i+1}^{k-1} (P_0^j (1 - P_0^j - P_1^j)) \right) (1 - P_0^k - P_1^k P_0^k).$$

6. OTHER STATISTICAL PROPERTIES

Once we find the probability of a dose being chosen as MTD (Section 4) and the expected number of patients treated at each dose level (Section 5), other important statistical properties can be found easily as follows.

The target toxicity level (TTL) is the dose limiting toxicity at MTD.

$$\begin{aligned} \text{TTL} &= P(\text{toxicity at MTD} | \text{dose } 1 \leq \text{MTD} < \text{dose } n) \\ &= \sum_{i=1}^{n-1} P(\text{toxicity at MTD} | \text{MTD} = \text{Dose } i) P(\text{MTD} = \text{Dose } i | \text{dose } 1 \leq \text{MTD} < \text{dose } n) \\ &= \frac{\sum_{i=1}^{n-1} p_i P(\text{MTD} = \text{Dose } i)}{\sum_{i=1}^{n-1} P(\text{MTD} = \text{Dose } i)}. \end{aligned}$$

For $1 \leq j \leq n$, let Y_j be the number of toxicity at dose j and X_j be the number of patients

treated at dose level j , then the expected number of toxicity at dose level j is

$$E(Y_j) = E(X_j)P(\text{toxicity at dose } j) = p_j E(X_j),$$

and the expected overall toxicity in a trial = $\sum_{i=1}^n E(X_i)P(\text{toxicity at dose } i) = \sum_{i=1}^n p_i E(X_i)$.

7. EXAMPLES

To illustrate, we give two examples encountered in the our experience: a 3+3 design without dose de-escalation, and a 3+6 design with dose de-escalation. We used the Splus program *pmtd*, which is written by the authors and available at <http://www2.umdnj.edu/~linyo>, to do all the calculation.

7.1. Example 1: 3 + 3 design without dose de-escalation

This trial is a phase I study of sequential topoisomerase I/topoisomerase II therapy for patients with high-risk acute non-lymphocytic leukemia [Strair *et al.* 1999]. It is designed to determine the MTD and DLT of etoposide (the topo II drug) administered as a daily infusion for three consecutive days after the completion of cytarabine-topotecan (the topo I regimen).

Groups of 3 patients will be entered at a dose level. If all 3 patients treated at a dose level have been observed for 28 days without DLT, then the dose will be escalated (dose levels are given in Table 1). If at least 2/3 patients have DLT, then the previous dose level will be considered as the MTD. If 1/3 patients have DLT, then 3 more patients will be treated at this dose level. If none of these patients has DLT, then the dose will be escalated. If at least one of the 3 additional patients has DLT, then the previous dose will be considered the MTD.

Note that if dose escalation is still indicated at the last (i.e., the highest) dose level 6, then the MTD is at or above the last dose level. If the trial stops at the first dose (at least 2 out of 3

Table 1. *Three scenarios of probabilities of toxicity at dose levels*

Dose level	1	2	3	4	5	6
mg/m ²	60	80	100	120	140	160
Probability of Toxicity						
First Scenario	0.05	0.10	0.15	0.25	0.35	0.50
Second Scenario	0.25	0.30	0.35	0.45	0.55	0.60
Third Scenario	0.05	0.15	0.25	0.35	0.50	0.70

Table 2. *Probability that a dose level will be declared as the MTD*

Dose level	1	2	3	4	5	6
mg/m ²	60	80	100	120	140	160
First Scenario[†]						
Probability of Toxicity	0.05	0.10	0.15	0.25	0.35	0.50
Probability that the dose is declared as MTD	0.09	0.16	0.29	0.26	0.14	0.00
Second Scenario[‡]						
Probability of Toxicity	0.25	0.30	0.35	0.45	0.55	0.60
Probability that the dose is declared as MTD	0.30	0.18	0.09	0.02	0.003	0.00
Third Scenario[*]						
Probability of Toxicity	0.05	0.15	0.25	0.35	0.50	0.70
Probability that the dose is declared as MTD	0.18	0.32	0.29	0.16	0.03	0.00
†: $P(\text{MTD} < 60 \text{ mg/m}^2) = 0.027$, $P(\text{MTD} \geq 160 \text{ mg/m}^2) = 0.029$, TTL = 18.9% for 1st scenario						
‡: $P(\text{MTD} < 60 \text{ mg/m}^2) = 0.400$, $P(\text{MTD} \geq 160 \text{ mg/m}^2) = 0.000$, TTL = 29.0% for 2nd scenario						
*: $P(\text{MTD} < 60 \text{ mg/m}^2) = 0.027$, $P(\text{MTD} \geq 160 \text{ mg/m}^2) = 0.001$, TTL = 20.4% for 3rd scenario						

patients or at least 2 out of 6 patients have DLT at the first dose level), then the MTD is below the first dose level. In either of the above cases, the MTD is not determined from the trial.

Table 1 gives three different scenarios for the probabilities of toxicity at the dose levels. The first scenario represents low starting toxicity, the second represents higher starting toxicity, and the third represents low starting toxicity and high toxicity at the last dose level. The third scenario is added as a result of our discussion with the investigator on the statistical properties found for the first two scenarios.

The probability that a dose level will be declared as the MTD is calculated in Table 2. From Table 2, the estimated target toxicity level (TTL, the probability of DLT at MTD) is 18.9% for

the first scenario, 29.0% for the second scenario and 20.4% for the third scenario. As shown, most likely 100 mg/m² dose will be declared as MTD for the first scenario, 60 mg/m² dose will be declared as MTD for the second scenario and 80 mg/m² dose will be declared as MTD for the third scenario.

Table 3 summarizes the expected number of patients and the expected number of toxicity incidences at each dose level. Table 3 shows that, on average, we expect to treat 16-17 patients and observe 2-3 incidences of DLT for the 1st scenario, 8-9 patients and observe 2-3 incidences of DLT for the 2nd scenario, and 13-14 patients and observe 2-3 incidences of DLT for the 3rd scenario. The expected overall toxicity rate is 17.5% (=2.83/16.17) for the first scenario, 29.5% (=2.59/8.76) for the second scenario, and 20.5% (=2.79/13.61) for the third scenario.

7.2. Example 2: 3 + 6 design with dose de-escalation

This is a phase I trial to determine the MTD and DLT of doxorubicin when given with 13-cis retinoic acid (CRA) and alpha interferon (INF-A) in patients with metastatic melanoma and advanced sarcoma [Aisner *et al.* 2000]. The doxorubicin dose escalation strategy is as follows. Groups of 3 patients will be entered at a dose level. If all 3 patients treated at a dose level completed the first cycle of therapy without DLT, then the dose will be escalated. If 1/3 patients have DLT, then 6 more patients will be treated at this dose level. If none of these additional patients has DLT, then the dose will be escalated. If at least one of the 6 additional patients has DLT, then 6 more patients are treated at the prior dose level (i.e., dose de-escalation), provided that only 3 patients were previously treated at that prior dose. The MTD is the dose level at which 0/9 or 1/9 patient experience DLT and that at least 2/3 or 2/9 patients treated with the next higher dose have had DLT. Note that if dose escalation is still indicated at the last (i.e., the highest) dose level, then the MTD is at or above the last dose level. If the trial stops at the first

Table 3. *Expected number of patients and expected number of toxicity incidences at each dose level*

Dose level	1	2	3	4	5	6	
mg/m ²	60	80	100	120	140	160	Total
First Scenario							
Probability of Toxicity	0.05	0.10	0.15	0.25	0.35	0.50	
Expected number of patients	3.41	3.63	3.51	3.06	1.87	0.70	16.17
Expected number of toxicity incidences	0.17	0.36	0.53	0.77	0.65	0.35	2.83
Second Scenario							
Probability of Toxicity	0.25	0.30	0.35	0.45	0.55	0.60	
Expected number of patients	4.27	2.59	1.28	0.50	0.11	0.01	8.76
Expected number of toxicity incidences	1.07	0.78	0.45	0.22	0.06	0.01	2.59
Third Scenario							
Probability of Toxicity	0.05	0.15	0.25	0.35	0.50	0.70	
Expected number of patients	3.41	3.87	3.38	2.06	0.78	0.12	13.61
Expected number of toxicity incidences	0.17	0.58	0.85	0.72	0.39	0.08	2.79
Expected overall toxicity rate = 17.5% for 1st scenario							
Expected overall toxicity rate = 29.5% for 2nd scenario							
Expected overall toxicity rate = 20.5% for 3rd scenario							

dose (at least 2/3 or 2/9 patients have DLT at the first dose level), then the MTD is below the first dose level. In either of the above cases, the MTD is not determined from the trial.

Table 4 gives two different scenarios for the probabilities of toxicity at the dose levels provided by the investigator through our discussion. The probability that a dose level will be declared as the MTD is calculated in Table 5. From Table 5, the estimated TTL is 10.2% and 12.9% for the first and second scenario, respectively.

Table 6 summarizes the expected number of patients and the expected number of toxicity incidences at each dose level. Table 6 shows that, on average, we expect to treat 16-17 patients and observe 2-3 incidences of DLT for the first scenario, and to treat 16-17 patients and observe 3-4 incidences of DLT for the second scenario. The expected overall toxicity rate is 15.2% (=2.50/16.4) and 18.6% (=3.02/16.27) for the first and second scenario, respectively.

Table 4. *Two scenarios of probabilities of toxicity at doxorubicin dose levels*

Dose level	1	2	3
mg/m ²	45	60	75
Probability of Toxicity			
First Scenario	0.05	0.15	0.30
Second Scenario	0.10	0.15	0.40

Table 5. *Probability that a doxorubicin dose level will be declared as the MTD*

Dose level	1	2	3
mg/m ²	45	60	75
First Scenario[†]			
Probability of Toxicity	0.05	0.15	0.30
Probability that the dose is declared as MTD	0.32	0.35	0.00
Second Scenario[‡]			
Probability of Toxicity	0.10	0.15	0.40
Probability that the dose is declared as MTD	0.29	0.39	0.00
†: $P(\text{MTD} < 45 \text{ mg/m}^2) = 0.053$, $P(\text{MTD} \geq 75 \text{ mg/m}^2) = 0.278$, TTL=10.2% for 1st scenario			
‡: $P(\text{MTD} < 45 \text{ mg/m}^2) = 0.173$, $P(\text{MTD} \geq 75 \text{ mg/m}^2) = 0.149$, TTL=12.9% for 2nd scenario			

Table 6. *Expected number of patients and expected number of toxicity incidences at each dose level*

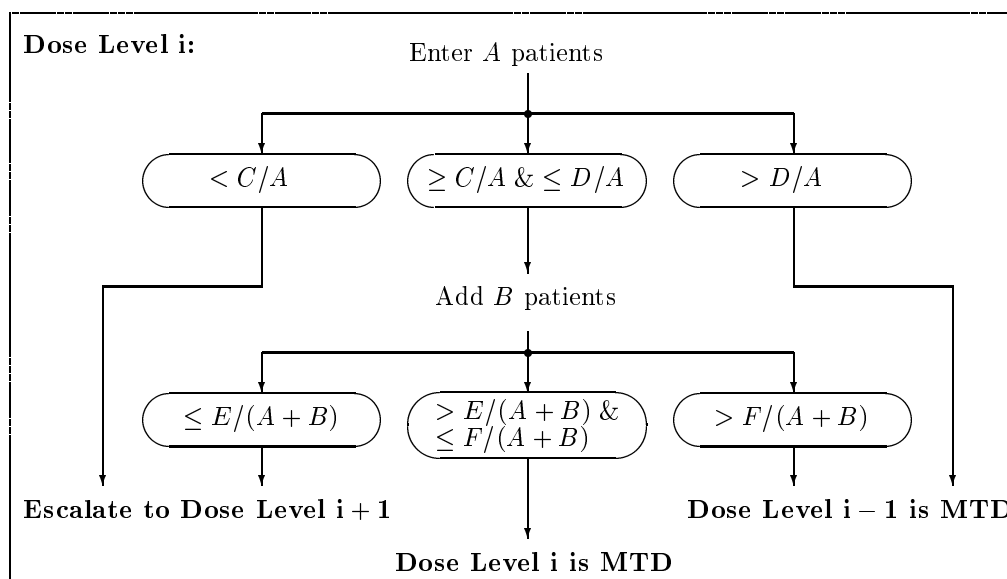
Dose level	1	2	3	
mg/m ²	45	60	75	Total
First Scenario				
Probability of Toxicity	0.05	0.15	0.30	
Expected number of patients	5.59	6.87	3.98	16.45
Expected number of toxicity incidences	0.28	1.03	1.19	2.50
Second Scenario				
Probability of Toxicity	0.10	0.15	0.40	
Expected number of patients	6.07	6.6	3.54	16.27
Expected number of toxicity incidences	0.61	1.00	1.41	3.02
Expected overall toxicity rate = 15.2% for 1st scenario				
Expected overall toxicity rate = 18.6% for 2nd scenario				

8. DISCUSSION

In this paper we have studied several key statistical properties for the algorithm-based design in its general framework based on the exact mathematical derivation. Although there is no single universally accepted standard method for Phase I cancer clinical trials, the algorithm-based traditional designs, especially the so-called ‘3+3’ design, are certainly the most commonly used. Our experience of applying the results of this paper in assisting clinical investigators, as illustrated by the examples, is that it helps them in gaining insight into the dose level selections for their studies during the design stage. Among several implications, such as the expected number of patients to be treated at each dose level, the paper has also clarified that the algorithm-based design does not have a fixed target toxicity level (TTL) (such as 33% for the ‘3+3’ design in many people’s misconception). We suggest considering several possible scenarios of the toxicity rate at each dose level and find out the TTLs when designing a Phase I algorithm-based trial. The general framework of the ‘A+B’ design with or without de-escalation in this paper has provided much needed flexibility in selecting an algorithm-based design.

It may have been noticed from Figs. 1 and 2 that the usual ‘A+B’ design always declares the previous dose $i - 1$ as the MTD when the criterion for dose i is met. This conservative approach always excludes the last dose from being the MTD, and its drawback can be seen from the results in Tables 2 and 5 at the last dose level, especially for Table 5 when there were only 3 levels of dose in the experiment. Actually the method used in this paper can be extended to a more general framework of design that allows the current dose i being declared as the MTD without any difficulty. We depict in Figure 3 such an extension, where the dose i is declared as the MTD when there are more than $E/(A + B)$ but no more than $F/(A + B)$ patients experienced DLT at dose level i .

Finally, we acknowledge that new Phase I clinical trial designs have been proposed over the

Fig. 3. Escalation Scheme for a more general $A + B$ design without dose de-escalation

past decade. Among these new designs, the Bayesian-based continual reassessment methods (CRM) have been advocated [O'Quigley *et al.* 1990, Whitehead and Brunier 1995, Babb *et al.* 1998, Heyd and Carlin 1999]. For these designs, it is also important to find the statistical properties discussed in this paper, such as the expected number of patients in the trial, the expected incidences of DLT, etc. Research in this direction is ongoing.

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REFERENCES

- BABB, J., BOGATKO, A. and ZACKS, S. (1998). *Cancer phase I clinical trials: efficient dose escalation with overdose control*, *Statistics in Medicine*, **17**, 1103-1120.
- CARTER, S. K. (1987). *The phase I study*, in Hellmann K. K. and Carter S. K. (eds): *Fundamentals of Cancer Chemotherapy*. New York, McGraw Hill, 285-300.
- DENT, S. F. and EISENHAEUER, E. A. (1996). *Phase I trial design: Are new methodologies being put into practice?*, *Annals of Oncology*, **7**, 561-566.
- EDLER, L. (1990). *Statistical requirement of phase I studies*, *Onkologie*, **13**, 90-95.
- HEYD, J. M. and CARLIN, B. (1999). *Adaptive design improvements in the continual reassessment method for phase I studies*, *Statistics in Medicine*, **18**, 1307-1321.
- KORN, E. L., MIDTHUNE, D., CHEN, T. T., RUBINSTEIN, L. V., CHRISTIAN, M. C., and SIMON, R. M. (1994). *A comparison of two phase I trial designs*, *Statistics in Medicine*, **13**, 1799-1806.
- O'QUIGLEY, J., PEPE, M. and FISHER, L. (1990). *Continual reassessment method: a practical design for phase I clinical trials in cancer*, *Biometrics*, **46**, 33-48.
- SMITH, T. L., LEE, J. J., KANTARJIAN, H. M., LEGHA, S. S. and RABER, M. N. (1996). *Design and results of Phase I cancer clinical trials: Three-year experience at M.D. Anderson Cancer Center*, *Journal of Clinical Oncology*, **14**, No. 1., 287-295.
- STORER, B. E. (1989). *Design and analysis of phase I clinical trials*, *Biometrics*, **45**, 925-937.
- STRAIR, R., RUBIN, E., and AISNER, J. (1999). *A Phase I trial of sequential Topoisomerase I-Topoisomerase II inhibitor therapy for patients with high-risk non-lymphocytic leukemias*, Clinical trial protocol of The Cancer Institute of New Jersey.
- AISNER, J., AMJAD, M., and DiPAOLA, R. (2000). *A Phase I trial of chemosensitization with doxorubicin, 13-cis retinoic acid and alpha interferon in metastatic melanoma and advanced sarcoma*, Clinical trial protocol of The Cancer Institute of New Jersey.
- WHITEHEAD, J. and BRUNIER, H. (1995). *Bayesian decision procedures for dose determining experiments*, *Statistics in Medicine*, **14**, 885-893.