4
Dose-Finding in Oncology—Nonparametric Methods

ANASTASIA IVANOVA

4.1 Introduction

Phase I trials in oncology are conducted to obtain information on dose–toxicity relationship. Preclinical studies in animals define a dose with approximately 10% mortality (the murine LD_{10}). One-tenth or two-tenths of the murine equivalent of LD_{10}, expressed in milligrams per meters squared, is usually used as a starting dose in a Phase I trial. It is standard to choose a set of doses according to the modified Fibonacci sequence in which higher escalation steps have decreasing relative increments (100, 65, 50, 40, and 30% thereafter). Toxicity in oncology trials is graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (available online from the Cancer Therapy Evaluation Program website http://ctep.cancer.gov). Toxicity is measured on a scale from 0 to 5. The dose limiting toxicity (DLT) is usually defined as treatment related non-hematological toxicity of Grade 3 or higher, or treatment related hematological toxicity of Grade 4 or higher. The toxicity outcome is typically binary (DLT/no DLT). The underlying assumption is that the probability of toxicity is a nondecreasing function of dose. The maximally tolerated dose (MTD) is statistically defined as the dose at which the probability of toxicity is equal to the maximally tolerated level, Γ. Alternatively, the MTD can be defined as the dose just below the lowest dose level with unacceptable toxicity rate Γ_U, $\Gamma < \Gamma_U$ (Rosenberger and Haines 2002). For example, the MTD can be defined as the dose level just below the lowest dose level where two or more out of six patients had toxicity. In the first definition, the MTD can be uniquely determined for any monotone dose–toxicity relationship; in the second, the MTD depends on the set of doses chosen for the study. In Phase I oncology studies, Γ ranges from 0.1 to 0.35. In oncology, unlike many other areas of medicine, dose-finding trials do not treat healthy volunteers, but rather patients who are ill and for whom other treatments did not work. An important ethical issue to consider in designing such trials (Ratain et al. 1993) is the need to minimize the number of patients treated at toxic doses. Therefore, patients in oncology dose-finding trials are assigned sequentially starting with the lowest dose.

Von Békésy (1947) and Dixon and Mood (1954) described an up-and-down design where the dose level increases following a nontoxic response and decreases if toxicity is observed. This procedure clusters the treatment distribution around the dose for which the probability of toxicity is equal to $\Gamma = 0.5$. To target any quantile Γ, Derman (1957) modified the decision rule of the design using a biased coin. Durham and Flournoy (1994; 1995) considered two biased coin designs in the spirit of Derman. Wetherill (1963) and Tsutakawa (1967a, b) proposed to assign patients in groups rather than one at a time. Group up-and-down designs can target a wide range of toxicity rates, Γ. Storer (1989) and Korn et al. (1994) used decision rules of group designs to suggest several designs for dose finding. Among the designs studied in Storer (1989) and Korn et al. (1994) were versions of the traditional or $3 + 3$ design widely used in oncology.

Biased coin designs, group up-and-down designs, the traditional or $3 + 3$ design, and its extension A + B designs (Lin and Shih 2001) are often referred to as nonparametric designs. Nonparametric designs are attractive because they are easy to understand and implement since the decision rule is intuitive and does not involve complicated calculations. Designs such as the continual reassessment method (O'Quigley et al. 1990) and the escalation with overdose control (Babb et al. 1998) are often referred to as parametric designs.

In this chapter, we describe the $3 + 3$ design in Section 4.2. Basic properties of group up-and-down designs are given in Section 4.3. In Section 4.4, we review designs that use random sample size, such as the escalation and A + B designs. In Section 4.5, designs with fixed sample size are discussed. In Section 4.6, we describe more complex dose-finding situations such as trials with ordered groups and trials with more than one treatment.

4.2 Traditional or $3 + 3$ Design

The most widely used design in oncology is the traditional design also known as the standard or $3 + 3$ design. According to the $3 + 3$ design, subjects are assigned in groups of three starting with the lowest dose with the following provisions:

If only three patients have been assigned to the current dose so far, then:

- If no toxicities are observed in a cohort of three, the next three patients are assigned to the next higher dose level;
- If one toxicity is observed in a cohort of three, the next three patients are assigned to the same dose level;
- If two or more toxicities are observed at a dose, the MTD is considered to have been exceeded.

If six patients have been assigned to the current dose, then:

- If at most one toxicity is observed in six patients at the dose, the next three patients are assigned to the next higher dose level;

- If two or more toxicities are observed in six patients at the dose, the MTD is considered to have been exceeded.

The estimated MTD is the highest dose level with observed toxicity rate less than 0.33.

The properties of the 3 + 3 design will be discussed later. To understand this design better we first describe group up-and-down designs.

4.3 Basic Properties of Group Up-and-Down Designs

Let $D = \{d_1, \ldots, d_K\}$ be the set of dose levels selected for the study. Let $P(d)$ denote the probability of toxicity at dose d, $p_j = P(d_j)$. We assume that $P(d)$ is an increasing function of d. The *group up-and-down design* is defined as follows.

Subjects are treated in cohorts of size s starting with the lowest dose. Let $X(d_j)$ be the number of toxicities in the most recent cohort assigned to dose d_j, $X(d_j) \sim \text{Bin}(s, p_j)$. Let c_L and c_U be two integers such that $0 \le c_L < c_U \le s$. Assume that the most recent cohort of subjects was assigned to dose level d_j, $j = 1, \ldots, K$. Then

(i) if $X(d_j) \le c_L$, the next cohort of s subjects is assigned to dose d_{j+1};
(ii) if $c_L < X(d_j) < c_U$, the dose is repeated for the next cohort of s subjects;
(iii) if $X(d_j) \ge c_U$, the next cohort of s subjects is assigned to dose d_{j-1}.

Appropriate adjustments are made at the lowest and highest doses. The process is continued until N subjects are treated. We will denote this design as UD(s, c_L, c_U).

Gezmu and Flournoy (2006) showed that assignments in group up-and-down design are clustered around the dose with toxicity rate Γ_s, where Γ_s is the solution of

$$\Pr\{\text{Bin}(s, \Gamma_s) \le c_L\} = \Pr\{\text{Bin}(s, \Gamma_s) \ge c_U\}. \tag{4.1}$$

That is, if there is a dose d_k such that $\Gamma_s = p_k$, the assignments are clustered around d_k. If $p_{k-1} < \Gamma_s < p_k$, the assignments are clustered around dose $k - 1$ or k (Ivanova, 2004).

The parameters s, c_L and c_U in a group up-and-down design are chosen so that Γ is approximately equal to Γ_s, the solution of Eq. (4.1). To find Γ_s, one needs to write (4.1) using formulae for Binomial probabilities. For example, for UD($s, c_L = 0, c_U = 1$), Eq. (4.1) has the form $(1 - \Gamma_s)^s = 1 - (1 - \Gamma_s)^s$ with the solution $\Gamma_s = 1 - (0.5)^{1/s}$. For most of the group up-and-down designs, closed form solutions of Eq. (4.1) do not exist but approximations can be easily obtained. Examples of group up-and-down designs can be found in Section 4.5.

4.4 Designs that Use Random Sample Size: Escalation and A + B Designs

4.4.1 Escalation and A + B Designs

In this section, we describe two types of designs that are used in dose-finding studies in oncology and other areas. Both designs do not need specification of the total sample size, since, ideally, experimentation is continued until the MTD is exceeded by one dose level. *The escalation design* is defined as follows.

Subjects are assigned in groups of size m starting with the lowest dose. Let C_U be an integer such that $0 \leq C_U < m$. Let $X(d_j)$ be the number of toxicities in a cohort of subjects assigned to dose d_j. Assume that the most recent cohort of subjects was assigned to dose level d_j, $j = 1, \ldots, K-1$. Then

(i) if $X(d_j) \leq C_U$, the next cohort of m subjects is assigned to dose d_{j+1};
(ii) if $X(d_j) > C_U$, the trial is stopped.

The dose one level below the dose where $>C_U$ toxicities were observed is the estimated MTD.

The A + B design (Lin and Shih 2001) described below is a generalized version of the traditional or 3 + 3 design. It includes a stopping rule as in the escalation design but saves resources at lower doses. The design below does not allow dose de-escalation. We refer the reader to Lin and Shih (2001) for a description of A + B designs with the possibility of dose de-escalation. *The A + B design* is defined as follows.

Let A and B be positive integers. Let c_L, c_U, and C_U be integers such that $0 \leq c_L < c_U \leq \mathrm{A}$, $c_U - c_L \geq 2$, and $c_L \leq C_U < \mathrm{A} + \mathrm{B}$. Let $X_{\mathrm{A}}(d_j)$ be the number of toxicities in a cohort of size A assigned to dose d_j, and $X_{\mathrm{A+B}}(d_j)$ be the number of toxicities in a cohort of size A + B. Subjects are treated in cohorts of size A starting with the lowest dose. Assume that the most recent cohort was a cohort of A subjects that has been treated at dose d_j, $j = 1, \ldots, K-1$. Then

(i) if $X_{\mathrm{A}}(d_j) \leq c_L$, the next cohort of A subjects is assigned to dose d_{j+1};
(ii) if $c_L < X_{\mathrm{A}}(d_j) < c_U$, the cohort of B subjects is assigned to dose d_j; then, if in the combined cohort assigned to d_j, $X_{\mathrm{A+B}}(d_j) \leq C_U$, the next cohort of size A receives dose d_{j+1}, otherwise the trial is stopped.
(iii) if $X_{\mathrm{A}}(d_j) \geq c_U$, the trial is stopped.

The dose one level below the dose where unacceptable number of toxicities were observed ($\geq c_U$ toxicities in a cohort of size A or $>C_U$ toxicities in a cohort of size A + B) is the estimated MTD.

The escalation and A + B designs are constructed using general rules of group up-and-down designs. The escalation design is a group up-and-down design of the

form UD(m, C_U, $C_U + 1$), with large group size. The trial is stopped as soon as the design calls for dose de-escalation. The A + B design is a combination of two group up-and-down designs UD(A, c_L, c_U) with $c_U - c_L \geq 2$ and UD(A + B, C_U, $C_U + 1$). The experimenter switches to the second design every time the first design calls for repeating the dose. The trial is stopped as soon as either design calls for dose de-escalation. In both designs, the frequency of stopping escalation at a certain dose level depends on toxicity rate at this dose as well as on toxicity at all lower dose levels. Ivanova (2006) outlined the general principles of how to select parameters in the escalation and A + B designs. Parameter C_U in the escalation design can be chosen so that $(C_U + 1)/m = \Gamma_U$, if Γ_U is specified, or $C_U/m = \Gamma$, if Γ is specified. For example, if $\Gamma_U = 0.33$, escalation design with $m = 6$ and $C_U = 1$ can be used.

Several A + B designs are presented in Table 4.1. The approximate range for Γ and the approximate value of Γ_U were computed as described in Ivanova (2006).

Table 4.1. Examples of A + B designs

Design parameters	Γ	Γ_U
A = B = 3, $c_L = 0$, $c_U = 2$, $C_U = 1$	$0.17 < \Gamma < 0.26$	$\Gamma_U = 0.33$
A = B = 4, $c_L = 0$, $c_U = 3$, $C_U = 2$	$0.25 < \Gamma < 0.31$	$\Gamma_U = 0.38$
A = B = 4, $c_L = 1$, $c_U = 3$, $C_U = 3$	$0.37 < \Gamma < 0.44$	$\Gamma_U = 0.50$
A = B = 5, $c_L = 0$, $c_U = 2$, $C_U = 1$	$0.10 < \Gamma < 0.15$	$\Gamma_U = 0.20$
A = B = 5, $c_L = 0$, $c_U = 3$, $C_U = 2$	$0.20 < \Gamma < 0.25$	$\Gamma_U = 0.30$
A = B = 5, $c_L = 1$, $c_U = 3$, $C_U = 3$	$0.30 < \Gamma < 0.35$	$\Gamma_U = 0.40$

4.4.2 The 3 + 3 Design as an A + B Design

The 3 + 3 design described in Section 4.2 can be found in Table 4.1 (Design 1). The dose most frequently selected by the 3 + 3 design has a toxicity rate above 0.17 and below 0.26 approximately. Simulation studies (Reiner et al. 1999; Lin et al. 2001) showed that the 3 + 3 design selects the dose with toxicity rate near 0.2. The approximate upper bound $\Gamma_U = 0.33$ of the probability of toxicity at the dose selected by the design is often quoted when the 3 + 3 design is described.

4.5 Designs that Use Fixed Sample Size

A trial with relatively large fixed sample size allows assigning a number of patients in the neighborhood of the MTD. The disadvantage of using a fixed sample size is that the starting dose can be too low and the sample size might not be large enough to observe a single toxic outcome in the trial or the number of toxicities in the trial might not be large enough to estimate the MTD well. The sample size usually varies from 18 to 36.

4.5.1 Group Up-and-Down Designs

In Section 4.3, we described the group up-and-down design and mentioned that the assignments for the design are clustered around the dose with probability of toxicity Γ, where Γ is the solution of Eq. (4.1). Recommended designs for different quantiles are given in Table 4.2. If the target toxicity rate is low, the group size needs to be rather large. For example, for $\Gamma = 0.1$ the group up-and-down with the smallest group size is UD($s = 6, 0, 1$). Often approximations of Γ need to be used. For example, the recommended designs for $\Gamma = 0.20$ are UD(3, 0, 1) with $\Gamma_s \approx 0.21$ or UD(5, 0, 2) with $\Gamma_s \approx 0.22$.

Table 4.2. Examples of group up-and-down designs

Targeted quantile	Group up-and-down design
$\Gamma = 0.10$	UD(6, 0, 1) with $\Gamma_s \approx 0.11$
$\Gamma = 0.20$	UD(3, 0, 1) with $\Gamma_s \approx 0.21$
	UD(5, 0, 2) with $\Gamma_s \approx 0.22$
	UD(6, 0, 2) with $\Gamma_s \approx 0.18$
$\Gamma = 0.25$	UD(4, 0, 2) with $\Gamma_s \approx 0.27$
	UD(6, 0, 3) with $\Gamma_s \approx 0.25$
$\Gamma = 0.30$	UD(2, 0, 1) with $\Gamma_s \approx 0.29$
	UD(4, 0, 2) with $\Gamma_s \approx 0.27$
	UD(5, 1, 2) with $\Gamma_s \approx 0.31$
	UD(6, 1, 3) with $\Gamma_s \approx 0.34$
$\Gamma = 0.50$	UD(1, 0, 1)* UD(4, 1, 3)*
	UD(2, 0, 2)* UD(5, 1, 4)*
	UD(3, 0, 3)* UD(6, 2, 4)*

*Targeted quantile Γ_s is exactly 0.50 for these designs.

4.5.2 Fully Sequential Designs for Phase I Clinical Trials

In a clinical setting, assigning subjects one at a time may be necessary due to time and logistical constraints. The biased coin designs (Durham et al. 1994; 1995) use the most recent outcome and a biased coin to determine the assignment of the next patient. These designs lose efficiency since they use the information from the most recent patient only. The moving average design (Ivanova et al. 2003) uses information from several subjects that have been assigned at the current dose and hence is more efficient than the biased coin designs. The moving average design has a decision rule of a group up-and-down design but uses data from the s most recent subjects instead of a new group of subjects.

4.5.3 Estimation of the MTD After the Trial

Designs that use fixed sample size require specifying an estimation procedure to use after the trial is completed. It had been shown by simulations that the isotonic regression based estimator works better than other estimators (Stylianou and Flournoy 2002; Ivanova et al. 2003). The isotonic regression estimator is

essentially the maximum likelihood estimator for the isotonic model of the data. Let $N(d_j, n)$ be the number of patients assigned to dose d_j and $X(d_j, n)$ the number of toxicities at d_j after n patients have been dosed. Let $\hat{p}_j = X(d_j, n)/N_j(n)$ for all $j \in \{1, \ldots, K\}$ for which $X(d_j, n) > 0$, and $(\hat{p}_1, \ldots, \hat{p}_K)$ be the vector of these proportions. The vector of isotonic estimates $(\tilde{p}_1, \ldots, \tilde{p}_K)$ can be obtained from $(\hat{p}_1, \ldots, \hat{p}_K)$ by using the pool adjacent violators algorithm (Barlow et al. 1972). Stylianou and Flournoy (2002) described this process in detail. The dose with the value $\tilde{p}_i$ closest to Γ is the estimated MTD. If there are two of such values, the lowest of the doses is chosen except for the case where both doses have toxicity lower than Γ, in which case the higher of the two is chosen. Some authors suggested linear (Stylianou and Flournoy 2002) or logit interpolation (Ivanova et al. 2003). Methods that use interpolation allow for the estimated MTD to be between dose levels chosen for the trial.

4.6 More Complex Dose-Finding Trials

4.6.1 Trials with Ordered Groups

Sometimes patients can be stratified into two populations with possibly different susceptibility to toxicity. For example, UGT1A1 genotype might predict the occurrence of severe neutropenia during irinotecan therapy (Innocenti et al. 2004). In a study conducted by Innocenti et al. (2004), three out of six patients with the TA indel 7/7 genotype developed grade 4 neutropenia compared to 3 among 53 other patients. The two populations are referred to as *ordered* since it can be said that the probability of toxicity for the population with genotype 7/7 is the same or greater than the probability of toxicity at the same dose for the second population. Equally, the MTD (mg/m^2) for irinotecan is lower for patients with 7/7 genotype compared to other patients. Since MTDs are different, two trials need to be conducted, one for each subgroup. If one of the populations is far less prevalent, it might not be feasible to conduct both trials. One solution is to combine the two trials in one with the goal of finding two MTDs, one for each group. A parametric approach to this problem was proposed by O'Quigley et al. (1999) and O'Quigley and Paoletti (2003). Ivanova and Wang (2006) described a nonparametric design for the problem with two ordered groups and up to K dose levels tested. Assume without loss of generality that the first group is more susceptible to toxicity than the second, $G_1 \geq G_2$. Let $P^{(1\geq 2)} = \{p_{ij}^{(1\geq 2)}\}$ be the bivariate isotonic regression estimator (Robertson et al., 1988) of the toxicity rate for the two groups, $i = 1, 2$, $j = 1, \ldots, K$, obtained under the assumption $G_1 \geq G_2$ and the assumption that the probability of toxicity in each group is nondecreasing with dose. Subjects are assigned one at a time starting with dose d_1. Suppose that the most recent subject was assigned to dose d_j. Let $\tilde{p} = p_{ij}^{(1\geq 2)}$ be the bivariate isotonic estimate of the probability of toxicity at the current dose with $i = 1$ or 2 according to the patient's group. The next subject from the same group is assigned to:

(i) dose d_{j+1}, if $\tilde{p} < \Gamma - \Delta$;

(ii) dose d_{j-1}, if $\tilde{p} > \Gamma + \Delta$;
(iii) dose d_j, if $\Gamma - \Delta \leq \tilde{p} \leq \Gamma + \Delta$.

Appropriate adjustments are made at the highest and lowest doses. Design parameter Δ was set to $\Delta = 0.05$.

4.6.2 *Trials with Multiple Agents*

It is common in oncology to treat patients with drug combinations. Often, the dose of one agent is fixed and the goal is to find the MTD of the other agent administered in combination. Sometimes, two or three doses of one of the agents are selected with the goal of finding the MTD of the second agent for each dose of the first agent. For example, Rowinsky et al. (1996) described a trial where five doses of topotecan and two doses of cisplatin were selected for the study. Since topotecan and cisplatin cause similar toxicities such as severe neutropenia and thrombocytopenia it was not possible to distinguish which drug caused toxicity. Ivanova and Wang (2004) suggested conducting a single trial that uses the assumption of toxicity monotonicity in both directions, that is, for each agent; toxicity is nondecreasing with dose when the dose of the other agent is fixed. Their nonparametric design for the problem uses the bivariate isotonic estimate of the probability of toxicity and is similar in spirit to the nonparametric design for ordered groups described in the previous section.

Thall et al. (2003) recently described a different setup for trials with multiple agents. The goal was to find one or more maximally tolerated combinations. Doses of both agents were increased simultaneously until the first toxicity was observed. Then nearby dose combinations were explored. They used a Bayesian (parametric) design with a five-parameter model.

4.7 Conclusion

Nonparametric designs are easy to understand by a practitioner and easier to use compared to parametric designs. These designs are flexible. Some, as the escalation and A + B designs, have an embedded stopping rule, others require specification of the sample size. All the designs mentioned in this chapter can be constructed for a wide range of values Γ. Simulation studies are a good tool to choose the best design and adequate sample size for the planned study.

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