4 Dose-Finding in Oncology—Nonparametric Methods

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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, $\Gamma$. Alternatively, the MTD can be defined as the dose just below the lowest dose level with unacceptable toxicity rate $\Gamma_U$, $\Gamma < \Gamma_U$ (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, $\Gamma$ 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 $\Gamma$, 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, $\Gamma$. 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;