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Dose Finding in Oncology—Parametric Methods

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5.1 Introduction

The primary goal of a cancer Phase I clinical trial is to determine the dose of a new drug or combination of drugs for subsequent use in Phase II trials to evaluate its efficacy. The dose sought is typically referred to as the maximally tolerated dose (MTD) and its definition depends on the treatment under investigation, the severity and reversibility of its side effects, and on clinical attributes of the target patient population. Since it is generally assumed that toxicity is a prerequisite for optimal antitumor activity (see Wooley and Schein, 1979), the MTD of a cytotoxic agent typically corresponds to the highest dose associated with a tolerable level of toxicity. More precisely, the MTD \( \gamma \) is defined as the dose expected to produce some degree of medically unacceptable, dose limiting toxicity (DLT) in a specified proportion \( \theta \) of patients (see Gatsonis and Greenhouse, 1992). Hence, we have

\[
\text{Prob} \{ \text{DLT} | \text{Dose} = \gamma \} = \theta
\]

Due to the sequential nature of these trials, the small number of patients involved, and the severity of dose toxicity, designs with the following desirable properties are sought:

1. A priori information about the drug from animal studies or similar trials should be easily implemented in the entertained model.
2. The design should be adaptive (Storer, 1989), in the sense that uncertainty about the toxicity associated with the dose level to be given to the next patient (or cohort of patients) should be reduced when data collected thus far are taken into account.
3. The design should control the probability of overdosing patients at each stage.
4. The design should produce a sequence of doses that approaches the MTD as rapidly as possible.
5. The design should take into account the heterogeneity nature of cancer Phase I clinical trial patients.
A number of statistical designs have been proposed and extensively studied in the past three decades. Nonparametric approaches to this problem have been developed by Durham and Flournoy (1994) and Gasparini and Eisele (2000). Within a parametric framework, a model for the dose–toxicity relationship is typically specified and the unknown parameters are estimated sequentially. Bayesian approaches to estimating these parameters are natural candidates for designs that satisfy properties (1) and (2) above. Among such designs, we mention the pioneering work of Tsutakawa (1972, 1980), Grieve (1987), and Racine et al. (1986). More recent Bayesian models include the continual reassessment method (CRM) of O’Quigley et al. (1990), escalation with overdose control (EWOC) described by Babb et al. (1998), the decision-theoretic approach of Whitehead and Brunier (1995), and constrained Bayesian $C$- and $D$-optimal designs proposed by Haines et al. (2003). The CRM and EWOC schemes both produce consistent sequences of doses in the sense that the sequence of doses converge to the “true” MTD in probability but EWOC takes into account the ethical constraint of overdosing patients. The last two designs are optimal in the sense of maximizing the efficiency of the estimate of the MTD. A discussion on the performance of these designs can be found in Rosenberger and Haines (2002).

In this chapter, we focus in one particular parametric, adaptive, and Bayesian method—EWOC—and present two real life applications where this approach was used. EWOC is the first statistical method to directly incorporate formal safety constraints into the design of cancer Phase I trials. In Section 5.2, we show how the method controls the frequency of overdosing by selecting dose levels for use in the trial so that the predicted proportion of patients administered a dose exceeding the MTD is equal to a specified feasibility bound. This approach allows more patients to be treated with potentially therapeutic doses of a promising new agent and fewer patients to suffer the deleterious effects of a toxic dose. EWOC has been used to design over a dozen of Phase I studies approved by the Research Review Committee and the Institute Review Board of the Fox Chase Cancer Center, Philadelphia. Also, EWOC was adopted by the University of Miami for its National Cancer Institute Cancer Therapy Evaluation Program (NCI/CTEP) approved study of Cytochlor, a new radio-sensitizing agent synthesized at UM. Additionally, EWOC has been used in trials sponsored by pharmaceutical companies such as Pharmacia-Upjohn, Jensen, and Bristol-Myers-Squibb.

In Section 5.3, we show how EWOC permits the utilization of information concerning individual patient differences in susceptibility to treatment. The extension of EWOC to covariate utilization made it the first method described to design cancer clinical trials that not only guides dose escalation but also permits personalization of the dose level for each specific patient, see Babb and Rogatko (2001) and Cheng et al. (2004). The method adjusts doses according to patient-specific characteristics and allows the dose to be escalated as quickly as possible while safeguarding against overdosing. The extension of EWOC to covariate utilization was implemented in four FDA approved Phase I studies. Section 5.4 addresses the issue of the choice of prior distributions by exploring a wide range of vague and