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SEMIPARAMETRIC DOSE FINDING METHODS FOR PARTIALLY ORDERED DRUG COMBINATIONS

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Abstract: We investigate a statistical framework for Phase I clinical trials that test the safety of two or more agents in combination. For such studies, the traditional assumption of a simple monotonic relation between the dose and the probability of an adverse event no longer holds. Nonetheless, the dose toxicity (adverse event) relationship does obey an assumption of partial ordering in that there will be pairs of combinations for which the ordering of the toxicity probabilities is known. Some authors have considered how to best estimate the maximum tolerated dose (a dose providing a rate of toxicity as close as possible to some target rate) in this setting. A related and equally interesting problem is to partition the two-dimensional dose space into two sub-regions: doses with probabilities of toxicity lower and greater than the target. We carry out a detailed investigation of this problem, using the recently presented semiparametric dose finding method as the theoretical framework. This results in a number of proposals, one of which can be viewed as an extension of the product of independent beta probabilities escalation (PIPE) method. We derive useful asymptotic properties, which also apply to the PIPE method when it is seen as a special case of the more general method given here. Simulation studies provide added confidence concerning the good behavior of the operating characteristics.

Key words and phrases: Bayesian method, dose-finding design, partial ordering, phase I clinical trials, semiparametric method.

1. Introduction

The importance of multi-agent Phase I trials in drug development has grown in recent years. The practical benefits of drug combinations are numerous: several modes of action can be combined, or the negative side effects of one drug can potentially be attenuated by the presence of a second compound. The aim of Phase I oncology trials is to find one or more maximum tolerated dose (MTD) combinations that have a probability of toxicity as close as possible to some threshold α, specified in advance by clinicians (common values are 20%, 25%, and 33%). Algorithmic designs remain a popular approach to identifying the

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