Phase I design for oncology trials of drug combinations

Most of the current designs used for Phase I dose finding trials in oncology will either involve only a single agent or will impose some implicit ordering among the doses being investigated, based on perceived toxicity. The goal of the study is to estimate the maximum tolerated dose (MTD), the highest dose that can be administered with an acceptable level of toxicity. A key working assumption of these methods is the monotonicity of the dose–toxicity curve. In this talk, we consider situations in which the monotonicity assumption may fail. Our focus is on studies where there exist dose pairs for which the ordering of the toxicity probabilities cannot be known a priori. These studies are becoming increasingly common in practice, most notably, in phase I trials that involve drug combinations. We describe an extension of the continual reassessment method (CRM) for application to this type of problem. In relaxing the monotonicity assumption, the method is a generalization of the CRM, greatly increasing its ability to handle added complexity presented by modern dose finding problems.

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