A Hybrid Phase I-II/III Clinical Trial Design Allowing Dose Re-Optimization in Phase III

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ABSTRACT

Conventionally, evaluation of a new drug, A, is done in three phases. Phase I is based on toxicity to determine a "maximum tolerable dose" (MTD) of A, phase II is conducted to decide whether A at the MTD is promising in terms of response probability, and if so a large randomized phase III trial is conducted to compare A to a control treatment, C, usually based on survival time or progression free survival time. It is widely recognized that this paradigm has many flaws.

A recent approach combines the first two phases by conducting a phase I-II trial, which chooses an optimal dose based on both efficacy and toxicity, and evaluation of A at the selected optimal phase I-II dose then is done in a phase III trial. This paper proposes a new design paradigm, motivated by the possibility that the optimal phase I-II dose may not maximize mean survival time with A. We propose a hybridized design, which we call phase I-II/III, that combines phase I-II and phase III by allowing the chosen optimal phase I-II dose of A to be re-optimized based on survival time data from phase I-II patients and the first portion of phase III. The phase I-II/III design uses adaptive randomization in phase I-II, and relies on a mixture model for the survival time distribution as a function of efficacy, toxicity, and dose. A simulation study is presented to evaluate the phase I-II/III design and compare it to the usual approach that does not re-optimize the dose of A in phase III.