SIMULTANEOUSLY OPTIMIZING DOSE AND SCHEDULE OF A NEW CYTOTOXIC AGENT

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Recently, a new type of phase I design was proposed that determines a maximum tolerated schedule (MTS), rather than a conventional maximum tolerated dose (MTD), in which the MTS is defined as the maximum number of courses of a cytotoxic agent that can be given without causing unacceptable cumulative toxicity (Braun et al., *Biometrics*, 2005, 61: 335-343). We expand this previous work by providing methodology to simultaneously optimize both dose and schedule in a multi-course phase I setting.

Specifically, we evaluate J doses, $j = 1, 2, \ldots J$, and K nested schedules, each of which is a sequence of administration times. The hazard of toxicity for a single administration of dose j is parameterized as a triangle having base of length $b_j + c_j$ and area equal to a_j, with the height of the triangle, $2a_j/(b_j + c_j)$, occurring at $u = b_j$. The total cumulative hazard for any enrolled subject is simply the sum of the areas of the triangular hazards for each administration received before an interim analysis.

Prior to a new subject enrolling, we combine the interim information of enrolled subjects in a standard censored data likelihood and use Bayesian methods to adaptively update the $3J$ hazard parameter estimates, and thereby, the MTS. We examine our approach via simulations motivated by an actual clinical trial and show our algorithm has excellent operating characteristics in a trial of $N = 60$ patients seeking to find the best combination of $J = 3$ doses and $K = 4$ schedules.