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Title: *Dose Titration Algorithm Tuning (DTAT) — MTD_i should supplant 'the' MTD*

Abstract:

Background. Absent adaptive, individualized dose-finding in early-phase oncology trials, subsequent 'confirmatory' Phase III trials risk suboptimal dosing, with resulting loss of statistical power and reduced probability of technical success for the investigational therapy. While progress has been made toward explicitly adaptive dose-finding and quantitative modeling of dose-response relationships, most such work continues to be organized around a concept of 'the' maximum tolerated dose (MTD). I aim to demonstrate concretely how the aim of early-phase trials might be reconceived, not as 'dose-finding', but as *dose titration algorithm (DTA)*-finding.

Methods. A Phase I dosing study is simulated, for a notional cytotoxic chemotherapy drug, with neutropenia constituting the critical dose-limiting toxicity. The drug's population pharmacokinetics and myelosuppression dynamics are simulated using published parameter estimates for docetaxel. The amenability of this model to linearization is explored empirically. The properties of a simple DTA targeting neutrophil nadir of 500 cells/mm^3 using a Newton-Raphson heuristic are explored through simulation in 25 simulated study subjects.

Results. Individual-level myelosuppression dynamics in the simulation model approximately linearize under simple transformations of neutrophil concentration and drug dose. The simulated dose titration exhibits largely satisfactory convergence, with great variance in individualized optimal dosing. Some titration courses exhibit overshooting.

Conclusions. The large inter-individual variability in simulated optimal dosing underscores the need to replace 'the' MTD with an individualized concept of MTD_i. To illustrate this principle, the simplest possible DTA capable of realizing such a concept was demonstrated. Qualitative phenomena observed in this demonstration support discussion of the notion of *tuning* such algorithms. Although here illustrated specifically in relation to cytotoxic chemotherapy, the DTAT principle appears similarly applicable to Phase I studies of cancer immunotherapy and molecularly targeted agents.