Accelerated Titration Designs

Janet Dancey, Boris Freidlin and Larry Rubinstein

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Introduction

A decade ago, investigators in oncology had a clear interest in modifications to the standard phase 1 design to make it more efficient, to treat fewer patients at non-toxic dose levels (which may be less efficacious), and to increase the precision of phase 2 dose recommendations. This was the conclusion of the 1996 joint meeting of the U.S. National Cancer Institute and the European Organization for the Research and Treatment of Cancer (Arbuck, 1996 [1], and Eisenhauer, 2000 [2]). At approximately the same time, a review of the recent phase 1 oncology literature revealed that few investigators were making use of the innovative phase 1 trial designs developed over the previous decade (Dent, 1996 [3]), meant to accomplish these very objectives.

Approximately five years previous to this, Sheiner published a series of papers in which he argued for the use of dose-response models in the analysis of phase 1 trials (Sheiner 1989, 1990 and 1991 [4-6]). Standard practice in oncology trials, among other fields, was to analyze the dose-toxicity relationship only in terms of the population as a whole, and to analyze it separately for each dose. Rarely were attempts made to fit a dose-toxicity model to the phase 1 data that accounted for inter-patient and intra-patient variability separately, accommodated the possibility of cumulative toxicity, and allowed for the construction of dose-toxicity curves for the sensitive as well as the typical patients. In addition, Sheiner argued for the use of intra-patient dose escalation, to maximize the possibility of individual patients receiving efficacious doses, and to increase the accuracy of the analysis of the phase 1 data. This was not commonly practiced in oncology phase 1 trials.

In response to the above, Simon et al (1997) [7] developed a family of “accelerated titration designs” and proposed use of an accompanying dose-toxicity model, based on the work of Sheiner [4, 5]. The main distinguishing features of these designs are (1) a rapid initial escalation phase; (2) intra-patient dose escalation; and (3) the ability to analyze trial results using a dose-toxicity model that incorporates parameters for intra-patient and inter-patient variation in toxicity and cumulative toxicity. The distinguishing features of the model are its simplicity, as well as the incorporation of separate variables for inter-patient and intra-patient variability, as well as for the possibility of cumulative toxicity.

Design

Simon et al [7] proposed a family of accelerated titration dose escalation designs. In their formulation all designs use 40% dose escalation steps. The dose escalation/de-escalation rules are based on definitions of dose-limiting toxicity (DLT) and of "moderate" toxicity. These definitions may be protocol specific. For example, Simon et al used any grade 2 toxicity that was considered treatment related as moderate toxicity. For purposes of comparison, they designated the standard phase 1 design (with 40% escalation steps in place of the standard modified Fibonacci escalation) as “Design 1”. They then introduced accelerated designs designated as “Design 1,” “Design 2” or “Design 3.”

Design 1 dictates that patients are dose escalated in cohorts of three until DLT is observed. One instance of DLT leads to treatment of three additional patients at the current dose level (with escalation continuing if no additional DLT is observed). Two instances of DLT, at a dose level, leads to a halt in dose escalation, with the prior dose level declared the MTD, so long as six patients have been treated at that level, with one instance of DLT (de-escalation continues until such a dose level is determined).

Design 2 starts with an accelerated phase that uses single patient cohorts per dose level. When the first instance of first-course DLT is observed, or the second instance of first-

course moderate toxicity is observed, the cohort for the current dose level is expanded to three patients and the trial reverts to use of design 1 for further cohorts.

Design 3 is similar to design 2 except that double dose steps are used during the accelerated phase. Two 40% dose steps correspond to approximately a doubling of the actual dose. The accelerated phase ends, as with design 2, when the first instance of first-course DLT or the second instance of first-course moderate toxicity is observed. After that, design 1 is used for further patients.

Design 4 is similar to design 3, except for the criterion that is used for triggering the end of the accelerated phase. With designs 2 and 3, the accelerated phase ends with the first-course instance of DLT or second instance of first-course moderate toxicity. With design 4, the trigger is the first instance of any-course DLT or the second instance of any-course intermediate toxicity. In addition, when the first instance of moderate toxicity is observed, two additional patients must have been treated at that dose, or a higher dose, (during any course) without experiencing moderate or worse toxicity, in order that the accelerated phase continue. This may require the treatment of one or two additional patients at that dose. Hence, design 4 may stop the accelerated phase earlier than design 3.

Table 1 summarizes the characteristics of the four dose escalation designs.

Intra-patient dose escalation

In order to maximize each patient's chance to be treated at the potentially active dose, the accelerated titration design allows intra-patient dose escalation for a patient who remains on study and has no evidence of toxicity at the current dose. Specifically, the dose for the next course is escalated if less than moderate toxicity was observed for the patient during the current course. If moderate toxicity occurred, then the dose stays the same for the next course for that patient. If DLT occurred, then the patient generally goes off study, but if not, then the dose is reduced. For design 2, single dose steps are used for intra-

patient dose changes. For designs 3 and 4, double dose steps are used for intra-patient dose changes during the accelerated stage, and single dose steps subsequently.

All four designs may be used with and without intra-patient dose escalation. Simon et al compared the performance of the four designs, with and without intra-patient dose escalation, in terms of toxicity, potential efficacy (reduction of treatment at doses below the MTD) and trial length. Table 1 also summarizes the two intra-patient dose escalation options.

Evaluation of performance

Simon et al [7] fit the above model to data from twenty phase 1 trials (involving 9 distinct agents). Only three of trials showed any evidence of cumulative toxicity ($\alpha>0$). The estimates of α for the other trials were zero or very close to zero. The trials varied substantially in the other parameters and thus provide a broad range of experience for evaluation of the accelerated titration designs.

Simon et al [7] evaluated the performance of the accelerated titration designs by simulating phase I data based on the twenty sets of parameters estimated from the twenty real trials that they studied. For each of the twenty sets of parameters, they generated data for 1000 phase I trials and applied each of their designs to the simulated data. Figure 1 shows the average number of patients per trial utilized by each of the designs. For each design, the average is taken over the same 20,000 simulated data sets generated from the sets of parameters derived from the twenty actual trials analyzed. Results for eight designs are shown. Designs 1-4 are as described above. The designs labeled with B utilize intra-patient dose escalation if the toxicity in the previous course is less than intermediate. Designs labeled with A do not permit intra-patient dose escalation.

Design 1A corresponds to the standard design, although it does not use Fibonacci dose steps. Design 1B is the standard design augmented to permit intra-patient dose escalation.

As can be seen in Figure 1, the average number of patients is much greater for the standard design 1A or 1B than for any of the accelerated titration designs. The average number of patients is somewhat less for designs 3 and 4 that use double dose steps compared to design 2. Although the average differences are not great, the differences for individual trials can be. That is, for a trial in which the starting dose is very low relative to the dose at which intermediate toxicity is expected, designs 2 and 3 will require substantially fewer patients.

Figure 1 also shows the average number of patient cohorts utilized by each design. The average is lowest for designs 3 and 4, which use double dose steps. Although the difference in average number of cohorts is not large, the difference in average time to complete the trials will be much shorter for designs 2 - 4 if patients are not instantaneously available, since the accelerated phase of those designs requires only one patient per cohort.

Figure 2 shows the average number of patients experiencing each level of toxicity as their worst toxicity during their treatment on the trial. With the standard design, an average of twenty-three patients experience less than intermediate toxicity (labeled “no toxicity” in the figure). These patients are under-treated. For design 2B the average number of under-treated patients is about eight and for designs 3B and 4B the number is less than five. This major reduction in the number of under-treated patients is achieved with very small increases in the average number of patients experiencing DLT or unacceptable toxicity with the accelerated titration designs. Figure 3 shows the average percentage of patients experiencing each level of toxicity as their worst toxicity during their treatment on the trial.

The accelerated titration designs without intra-patient dose escalation, 2A, 3A and 4A, performed quite well with regard to reduction in average number of patients and reduction of number of under-treated patients. They do not provide patients accrued early in the trial a full opportunity to be treated at a therapeutic dose, however. They are also

less effective in situations where inter-patient variability in susceptibility to toxicity is large.

These designs may be attractive, however, when there is concern about cumulative toxicity. It is worth noting, in this regard, that analysis of the twenty phase 1 trials used for evaluation of these designs revealed no evidence of ill effect from intra-patient dose escalation and lead the investigators to conclude that "cumulative toxicity does not appear to be a valid reason to prohibit intra-patient dose escalation, as it occurs rarely" (Arbuck, 1996 [1]).

To further illustrate the efficiency of the accelerated designs in comparison with the standard, we give in Figure 4 a simulated comparison of the performance of design 4B versus design 1A for a particular dose-toxicity model. The accelerated design completes the trial with less than half the number of patients required by the standard. More dramatically, due to the single-patient cohorts and two-step escalations, it requires only one patient for every six of the standard design to escalate through the portion of the dose-toxicity curve where DLT is unlikely. Of course, if the initial dose of the trial is not defined so conservatively, the comparison is not so extreme.

Model based analysis

By using a model for the statistical distribution of toxicity, based on current and previous doses, a graded toxicity scale, based on the unobserved continuous variable associated with toxicity, and multi-course treatment results, the accelerated titration designs allow for an efficient approach to analysis of phase 1 data. The model used in Simon et al, was based on measuring the worst toxicity experience for each patient during each course of treatment. That is, the model does not consider separate toxicity for each organ system, but takes the maximum over all organ systems and records that worst toxicity separately for each course of treatment for each patient. The model was designed to represent

different levels of worst toxicity. The toxicity experienced in a particular course was determined by the current dose administered and the total dose administered in the previous courses. The model incorporated parameters for both intra-patient and inter-patient variability, and for cumulative toxicity.

Suppose that the i^{th} patient receives dose d_{ij} during dose j and received a total dose D_{ij} for courses prior to j. Let α represent the effect of cumulative toxicity (α=0 indicates no effect of cumulative toxicity). Random variable β_i represents inter-patient variability in toxic effects; β_i is taken to be normally distributed with mean zero and variance σ_β^2. Random variable ε_{ij} represents intra-patient variability in toxic response; ε_{ij} is taken to be normally distributed with mean zero and variance σ_ε^2. These terms and random variables determine the unobserved magnitude y_{ij} of the worst toxicity for patient i in course j, according to the formula:

$$y_{ij} = \log\left(d_{ij} + \alpha D_{ij}\right) + \beta_i + \varepsilon_{ij}$$

In addition to the three parameters α, σ_β^2 and σ_ε^2, there are also several parameters for converting value y_{ij} into a graded level of toxicity. Values of y_{ij} less than K_1 correspond to less then moderate toxicity, values between K_1 and K_2 correspond to moderate toxicity, values between K_2 and K_3 correspond to dose limiting toxicity, and values greater than K_3 correspond to life-threatening toxicity. If one does not wish to distinguish DLT from life-threatening toxicity, then only K_1 and K_2 are needed. So there are 5-6 parameters to be estimated from the data. Table 2 summarizes the characteristics of the model. This model is a generalization of the K_{max} model of Sheiner et al [5], and of the model of Chou and Talalay [8, 9].

Given the data of the grade of toxicity (worst over organ systems) for each course of each patient, the method of maximum likelihood is used to estimate the model parameters. Splus software for fitting the parameters is available at http://linus.nci.nih.gov/~brb. That web site also contains an Excel macro for managing dose assignments to patients during

Accelerated Titration Design trials. The macro assists investigators in quality controlling the dose assignment and provides a convenient way of recording dose assignments in a systematic manner that makes the data available for subsequent analysis.

Figure 5 illustrates the power of the model based analysis to construct a dose-toxicity curve, not only for the typical patient (50^{th} percentile), but also for the patient who falls one standard deviation below the typical in terms of increased susceptibility to toxicity (16^{th} percentile). The standard approach to defining the MTD is based on the probability of toxicity at a given dose for the population as a whole, which often roughly corresponds to the probability of toxicity for the typical patient. With this approach, the initial phase 2 dose would be set, for Figure 5, at dose level 16 or 17, to keep the probability of DLT below 30%. However, the model based analysis reveals that such a dose level results in at least 40% - 60% likelihood of DLT for a non-trivial subgroup of the patient population (those at the 16^{th} percentile or below). This might suggest that a more prudent approach would be to define a lower initial phase 2 dose, to accommodate the susceptibility of this subgroup.

Figure 6 illustrates the power of the model based analysis to construct comparative dose-toxicity curves for the different levels of toxicity. For example, the analysis suggests that the dose-toxicity curves for grade 2 vs. grade 3 toxicity are separated by approximately four dose levels. This indicates that for a given patient, as well as for the population as a whole, DLT is likely to occur approximately four dose levels beyond moderate toxicity, suggesting that accelerated dose-escalation is likely to be safe, both for the population and for a given individual. Even though the dose-toxicity curve for DLT is relatively steep, it is well separated from the curve for moderate toxicity.

Sheiner [4, 5] proposed the use of dose-toxicity models for phase 1 trials a decade ago. They are still rarely used, despite their potential for facilitating the definition of a phase 2 starting dose.

Clinical Applications

First-in-man phase 1 trial designs of oncology agents share the following characteristics: selection of a "safe" starting dose, sequential dose escalation in cohorts of patients, and determination of a recommended dose based on a pre-specified primary endpoint, usually the occurrence of unacceptable toxicity in a defined number of patients treated at a given dose level. Optimal phase 1 designs result in the identification of a dose for further evaluation in a manner which is both safe and efficient. Higher starting doses, fewer patients per dose level and large escalation steps require fewer patients overall. However, safety is enhanced by lower starting doses, more patients per dose level to assure safety of the dose, and smaller dosing increments. Phase 1 designs must strike a balance between these elements. Accelerated titration designs proposed by Simon use the following modifications to enhance efficiency: as few as 1 patient per level to be enrolled and initial dose escalation steps are larger (e.g. 100% increments in the absence of toxicity). The number of patients per dose level increases to 3, once toxicity of a minimum degree (e.g. second instance of grade 2; first instance of DLT) has been seen in at least one patient. Thereafter a minimum of 3 patients in each cohort are recruited, expanding to 6 in the event one of 3 has a DLT in the protocol prescribed observation period (usually one cycle or 4-8 weeks of chronic therapy) and the dose escalation increments are reduced.

To assess the use and utility of the Accelerated Titration Designs in the evaluation of novel oncology therapeutics, we conducted a literature search using the ISI Web of Knowledge™ Database (Thomson ISI, Thomson Corporation, Philadelphia PA) in May and August 2005. All articles in the database that cited the original paper by Simon et al were retrieved and reviewed. In total, 106 publications were identified. Articles which

focused on statistical methodology of phase 1 studies (10), were not of phase 1 studies (4), that evaluated combinations of agents (12), were review articles (34), or of phase 1 studies that did not use the Simon [7] Accelerated Titration Designs (10) were not included in our review. In total, 36 publications of phase 1 trials of novel cancer therapeutics were identified. From the trial publications, the following details were abstracted: agent/class, schedule, type of design, study specific modifications to the design (e.g. patients/cohort and dose escalation increments during the accelerated phase, rules for terminating the accelerated phase, dose escalation increments following termination of the accelerated phase, dose levels evaluated, and the number of dose levels evaluated during the accelerated phase and subsequently). A summary of these trials are provided in Table 3 and Table 4.

From the results of our review a number of observations can be made regarding the utilization of the designs. First, the classes of agents selected for evaluation using an accelerated titration design favor agents that belong to chemical classes that have been previously study, or to biological agents not associated with significant risk of severe, irreversible organ toxicity. This is not surprising, as agents with these characteristics would engender a level of comfort regarding the safety of using an accelerated titration design. Second, designs 3 and 4, which utilize single patient cohorts and 100% dose escalations, are the most commonly used. Third, almost half the studies do not utilize intra-patient dose escalation. Fourth, the most common modifications to the designs are those determining the dose escalation increments following termination of the accelerated phase and/or modifications to rules for terminating the accelerated phase. Most trials with modifications in the dose increments following termination of the accelerated phase stipulated dose increments of 15-30% rather than 40%. A few utilized higher dose increments (50-67%) and a few reverted to a modified Fibonacci escalation schema. Rules for terminating the accelerated phase included the first occurrence of any toxicity, or the achievement of a pre-specified dose (e.g. mouse equivalent MTD). Given the frequency and nature of these modifications, it appears that investigators retain concerns regarding the safety of the accelerated titration design dose escalation increments and termination rules.

To assess the efficiency and safety of the accelerated designs, the numbers of patients and dose levels, overall and during the accelerated phase were evaluated across the 36 studies. Patients treated above the ultimately recommended phase 2 dose (RP2D) were identified. If a patient was treated at a dose level prescribed by the accelerated phase dose increase and that dose exceeded the RP2D, then the dose level was considered to have exceed the recommended dose due to the accelerated phase rules. Similarly, patients that died on study due to obvious or suspected treatment-related toxicity were identified. Those fatalities which occurred at doses prescribed during the accelerated phase of the study were classified as deaths during the accelerated phase. As summarized in Table 4, the accelerated titration designs, as used in these studies, rarely resulted in dose escalation beyond the recommended phase 2 dose. Only 4 of 36 exceed the recommended phase 2 dose during the accelerated titration phase, and only 1 death from toxicity occurred during the accelerated titration phase, among the 911 patients enrolled in these studies. (It should be noted, however, that the use of acceleration may have contributed, in some trials, to exceeding the RP2D by a greater number of doses, or for a greater number of patients, than would otherwise have happened. Thus, the use of acceleration, in these trials, may have increased the over-all number of patients treated above the RP2D, even beyond the acceleration phase itself, and thus contributed to a greater death rate from toxicity.) Based on its utilization in these selected studies, the accelerated titration design appears to provide an enhanced efficiency with acceptable safety. However, there are a number of issues investigators might consider prior to selecting an accelerated titration design to evaluate a novel agent in a first-in-man phase 1 clinical trial.

The use of minimum one patient cohorts and larger dose escalation steps may be advantageous under the following circumstances: (1) the agent is of a chemical class that has been widely studied, (2) the agent is predicted to have minimal inter-patient variability in pharmacokinetics, (3) the agent's anticipated toxicity is unlikely to be

severe or irreversible, and is amenable to close monitoring and supportive interventions. Examples of agents most amenable to evaluation using a phase 1 accelerated titration design might be the following: a new formulation of a previously studied agent (e.g. liposomal formulation of paclitaxel), a biological agent with minimal toxicity based on animal models (e.g. antibody or small molecule inhibitor of a receptor tyrosine kinase inhibitor), or an agent for which significant interspecies variability in preclinical toxicology has led to a very conservative starting dose in human phase 1 study. Under these circumstances, the increased efficiency and presumed safety of an accelerated design might make it preferable.

Conversely, there are situations where an accelerated titration design may not provide the optimal balance between safety and efficiency as either larger numbers of patients/dose cohort and/or smaller dose increments would be preferable. Agents associated with steep-dose response curves for toxicity, severe irreversible toxicity, unexplained mortality in animal toxicology studies, or large variability in doses or plasma drug levels eliciting effects, may require alternative designs to optimally balance safety and efficiency. For example, larger patient numbers/dose cohort may be preferred if there is anticipated wide inter-patient variability in toxic effects due to pharmacokinetic or pharmacogenomic differences between patients. For this circumstance, larger patient numbers per dose level is appropriate since decisions about the safety of a given dose may require more than a single patient's experience. Similarly, when a pharmacokinetic or a pharmacodynamic endpoint, rather than toxicity, is the primary endpoint, larger numbers of patients per dose level are recommended due to anticipated inter-patient

variability in these endpoints. With either situation, the use of an accelerated titration design with single patient cohorts may not be optimal.

There are also situations where the small dose escalation increments may be advisable. For example, if the agent is predicted to have severe, irreversible or potentially fatal organ toxicity based on animal toxicology, particularly if associated with a steep dose-response curve for toxicity, relatively small changes in dose/concentration may lead from minimal toxicity to severe toxicity, and thus smaller dose escalation increments are preferable to ensure safety.

Approaches to enhancing the proportion of patients in a phase 1 trial receiving "therapeutic" dose levels includes not only limiting enrolment on lower dose levels, but also allowing dose escalation within individual patients. Intra-patient dose escalation provides two advantages: it improves the likelihood of benefit from the agent for the individual patient and it increases the experience at higher dose levels. Accelerated titration designs proposed by Simon et al [7] allow intra-patient dose escalation if no toxicity > grade 1 was seen in the first cycle at the assigned dose level. While it did not appreciably shorten the study duration, it did allow more patients to be treated at, or near the recommended phase 2 dose and increased the number of cycles evaluated at the higher dose levels.

Although the rationale supporting intra-patient dose escalation is appealing, it does not seem to be widely applied. Thus, despite the appeal of escalating patients to higher doses

than they were assigned initially, should safety criteria be met, some issues remain with its routine application in phase 1 protocols. Many phase 1 protocols continue to be written prohibiting intra-patient escalation since it is believed to have minimal impact on trial efficiency while bringing with it concerns about practical issues regarding the "rules" for implementing dose escalation and safety. Studies that have allowed intra-patient escalation within their protocols have generally allowed dose escalation to occur after the patient has been evaluated at the current dose level for the duration of the observation period and that the patient has had minimal/no toxicity. Less commonly used, are rules which require not only that the patient has not had significant toxicity but also that the next higher dose level has been evaluated in one or more new patients, a more stringent and cumbersome criterion that may be favored to enhance safety and also to distinguish between acute versus cumulative toxic events. Although experience with intra-patient dose escalation within phase 1 studies is limited, to date its use within phase 1 studies using an accelerated titration design did not appear to compromise patient safety or complicate the interpretation of the study results. Of note, within a given protocol, it is important to require a minimum number of newly recruited patients at each dose level, and to base further dose escalation decisions upon the behaviour of the drug in these individuals.

Conclusions

Accelerated titration designs can dramatically reduce the number of patients accrued to a phase 1 trial, in comparison to the standard phase 1 design. They can also substantially shorten the duration of the phase 1 trial. With intra-patient dose escalation and

application of a dose-toxicity model, they provide much greater information than the standard design and analysis with regard to cumulative toxicity, inter-patient and intra-patient variability, steepness of the dose-toxicity curve, and separation of the dose-toxicity curves for the varying toxicity levels. They also provide all patients entered in the trial a maximum opportunity to be treated at a therapeutic dose.

Despite this, we find that the designs are not widely used, likely due to the conservativeness of investigators. Even when they are used, they are often used with an initial dose set much more conservatively than would be done for the standard design, and without use of intra-patient dose escalation, thereby reducing their effectiveness. A recent comprehensive review of the risk-benefit relationship for phase 1 trials conducted over the past decade reveals an over-all toxicity death rate of only .005 (Horstmann, 2005 [10]). An accompanying editorial (Kurzrock, 2005 [11]) argues that such a low toxicity death rate, in the context of treatment for an often rapidly fatal disease, suggests that phase 1 trials may be conducted in an overly cautious fashion. Appropriate utilization of designs such as the accelerated titration designs might increase the potential for benefit in phase 1 trials, with little increase in risk.

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Design	Description
1	Cohorts of 3 new patients per dose level. If 1 of 3 patients experiences DLT in first course, expand cohort to 6 patients.
2	Cohorts of 1 new patient per dose level. When first instance of first course DLT is observed, or second instance of first course grade 2 toxicity of any type, expand cohort for current dose level and revert to use of design 1 for all further cohorts.
3	Same as design 2 except that double dose steps are used during initial accelerated stage of trial (both for between patient and within patient escalations).
4	Cohorts of 1 new patient per dose level and double dose steps are used during the initial accelerated stage of the trial. When the first instance of DLT is observed at any course, or the second instance of any course grade 2 toxicity of any type, expand cohort for current dose level and revert to use of design 1 for all further cohorts. When the first instance of moderate toxicity is observed, two additional patients must have been treated at that dose, or a higher dose, (during any course) without experiencing moderate or worse toxicity, in order that the accelerated phase continue.
Escalation	**Description**
A	No within patient dose escalation. De-escalate if grade 3 or worse toxicity at previous course.
B	Escalate if grade 0-1 toxicity at previous course. De-escalate if grade 3 or worse toxicity at previous course.

Table 1: Summary of the 4 Dose Escalation Designs and the 2 Intra-Patient Dose Escalation Options

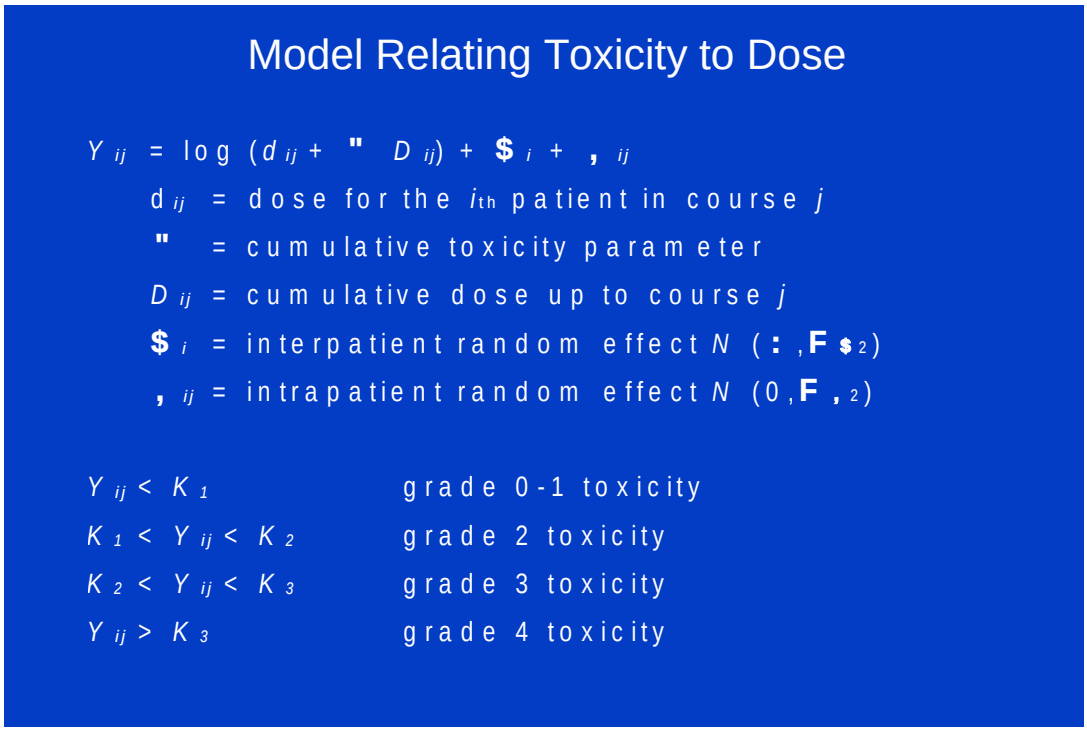

Table 2: Summary of the Dose-Toxicity Model for Both the Unobserved Continuous Toxicity Variable and the Observed Toxicity Grade Level

Author/Reference	Agent	Schedule	Design	Intrapatient Dose Escalation	Recommended Dose
LoRusso [12]	5-fluoro-pyrimidinone	orally daily for 5 days every 4 weeks	4B	Yes	625 mg/m2/day orally for 5 days every 4 weeks
Goetz [13]	17-(Allylamino)-17-demethoxygeldanamycin	i.v. weekly x 3 every 4 week	2B	Yes	308 mg/m2 weekly x 3 every 4 weeks
Grem [14]	17-(Allylamino)-17-demethoxygeldanamycin	1-hour i.v. infusion daily for 5 days every 3 weeks	2B	Yes	40 mg/m2 daily x 5 every 3 weeks
Sessa [15]	BBR3464, cationic triplatinum complex	i.v. daily x 5 every 3 weeks	4B	Yes	0.12 mg/m2 /day x 5 every 3 weeks
Mross [16]	BBR3576, aza-anthrapyrazole	i.v. infusion every 4 weeks.	4A	No	150mg/m2 every 4 weeks
Plummer [17]	BMS-184476, taxane analog	i.v. weekly x 3 every 4 weeks, later amended to weekly x 2 every 21 days.	4B	Yes	50 mg/m2/week x 2 every 21 days
Mani [18]	BMS-247550, derivative of Epothilone B	1-h i.v. infusion every 3 weeks	Modified 4B	Yes	40 mg/m2 every 3 weeks
Abraham [19]	BMS-247550, derivative of Epothilone B	1-h i.v. infusion daily x 5 every 21 days.	Modified 3B	Yes	6 mg/m2/day x 5 every 21 days
Gadgeel [20]	BMS-247550, derivative of Epothilone B	1-h i.v. infusion every 21 days	Modified 2B	Yes	40 mg/m2 every 21 days
Undevia [21]	CEP-2563, receptor tyrosine kinase inhibitor	1 h i.v. daily x 5 every 21 days	Modified 3B	Yes	256 mg/m2/day x 5 every 21 days
Hovstadius [22]	CHS 828, cyanoguanidine	orally once daily x 5 days every 4 weeks	4B	Yes	20 mg once daily for 5 days (100 mg/cycle) every 4 weeks
Rudek [23]	COL-3, matrix metalloproteinase inhibitor	orally daily	4A	No	36 mg/m2/d without sunblock
Syed [24]	COL-3, matrix metalloproteinase inhibitor	orally daily	2A	No	50 mg/m2/day
Rustin [25]	Combretastatin A4 phosphate, tubulin targeting agent	i.v. x 5 for 2 weeks every 3 weeks	Modified 4B	Yes	52 to 68 mg/m2 x 5 for 2 weeks every 3 weeks
Chatterjee [26]	DRF-1042, camptothecin analog	po daily x 5 for 2 weeks every 3 weeks	Modified 3B	Yes	80 mg/m2 x 5 for 2 weeks every 3 weeks
Villalona-Calero [27]	Ecteinascidin-743, tetrahydroisoquinoline alkaloid	i.v. daily x 5 every 3 weeks	Modified 3A	No	325 µg/m2/day daily x 5
Ko [28]	EMD 273066 (huKS-IL2) immunocytokine	i.v. daily x 3 every 4 weeks	Modified 4A	No	6.4 mg/m2/day x 3 every 4 weeks
Goel [29]	GEM231, oligonucleotide to type I regulatory subunit of protein kinase A	3-day (1 patient) or a 5-day continuous i.v. infusion	Modified 4A	No	120 mg/m2/day x 5 days
Chen [30]	GEM231, oligonucleotide to type I regulatory subunit of protein kinase A	2-hour i.v. infusions twice weekly	Modified 4A	No	240 mg/m2 twice weekly
Borchmann [31]	H22xKi-4, bispecific anti-CD30 and CD64 monoclonal antibody	i.v. days 1, 3, 5, 7 q21 days	4B	Yes	80 mg/m2 per cycle
Gadgeel [32]	KRN5500, spicamycin derivative	1-h i.v.daily x 5 every 3 weeks	2B	Yes	4.3 mg/m2/day x 5 every 3 weeks
Schoemaker [33]	MAG-CPT, polymer conjugate of camptothecin	i.v. infusion over 3 days every 4 weeks	Modified 2A	No	68 mg/m2/day for 3 days every 4 weeks
Matsumura [34]	MCC-465, doxorubicin PEG immunoliposome	1-h i.v. infusion every 3 weeks	ATD planned	No	32.5 mg/m2 every 3 weeks
Clive [35]	Antagonist G substance P analog	i.v. every 3 weeks until the target maximum plasma concentration of 10 microM then weekly,	Modified 4A	No	400 mg/m2 weekly 6-h i.v. infusion.

Matsumura [36]	NK911, micelle encapsulated doxorubicin	i.v. every 3 weeks	Modified 3A	No	50 mg/m2 every 3 weeks
de Jonge [37]	PNU-159548, alkylcycline	i.v. every 3 weeks (2 studies)	Modified 4B	Yes	12 and 14 mg/m2 i.v. every 3 weeks in HP and MP patients
Lockhart [38]	PNU-166196A, brostallicin, a nonalkylating DNA minor groove binder	i.v. weekly x 3 every 4 weeks	Modified 3B	Yes	2.4 mg/m2/week.
Ten Tije [39]	PNU-166196A, brostallicin, a nonalkylating DNA minor groove binder	i.v. every 3 weeks	3B	Yes	10 mg/m2/3 weeks
Dupont [40]	Ro 31-7453, oral cell-cycle Inhibitor	2 Schedules: once or twice daily x 5 every 21 days;	3A	No	560 mg/m2 or flat dose of 1,000 mg daily for 4 days for both schedules.
Salazar [41]	Ro 31-7453, oral cell-cycle Inhibitor	2 schedules orally every 12 hours for 7 days or 14 days every 4 weeks	4A	No	200 mg/m2 bid for 7 days; 125 mg/m2 bid for 14 days.
Wadler [42]	Triapine, ribonucleotide reductase inhibitor	96-hour continuous i.v. infusion every 3 weeks or every 2 weeks	4B	Yes	120 mg/m2/d every 2 weeks
Murren [43]	Triapine, ribonucleotide reductase inhibitor	2 h i.v. daily x 5 days every 4 weeks or every 2 weeks	Began as modified Fibronacci then 4B	Yes	96 mg/m2 by 2-h i.v. infusion daily for 5 days every 2 weeks
Jones [44]	Tazarotene, acetylenic retinoid	orally daily	Modified 3A	No	25.2 mg/day
Al-Batran [45]	Trofosfamide	orally in 3 doses per day for 3 weeks	1B	Yes	125 mg/m2 administered in 3 doses per day every 3 weeks
Dees [46]	UCN-01, tyrosine kinase inhibitor	1-3 hours i.v. infusion every 4 weeks	4A	No	95 mg/m2 over 3 hours
Goh [47]	ZD9331, thymidylate synthase inhibitor	i.v for 5 days every 21 days.	3A	No	25 mg/day

Table 3 Phase 1 Trials Using Accelerated Titration Design

				Total
Trials (n)				36
Patients (n)				911
	Type			Trials (n)
Design	1			1
	2			6
	3			10
	4			18
	Unknown			1
Intrapatient Dose Escalation				
	Yes			20
	No			16
Modifications	Yes			15
	No			11
Types of Modifications				
	Dose escalation during the Accelerated Phase			3
	Patients/cohort during the Accelerated Phase			2
	Rules for Termination of Accelerated Phase			8
	Dose Escalation Following Accelerated Phase			19
	During Accelerated Phase		For Study	
	Median	Range	Median	Range
Patients/study (n)	5	0-15	22	7-74
Dose Levels (n)	3	0-12	6	3-15
Fold Dose Range			16	2-320
Patients Treated Above RP2D	0	0-6	6	0-28
Dose Levels Above RP2D	0	0-1 (4 of 36 studies had a dose level that exceeded the RP2D during the ATD)	1	0-3
Deaths due to toxicity	0	0-1 (1 patient across all studies died due to toxicities)	0	0-3 (13 patients across all studies died due to toxicities)

Table 4. Summary of Phase 1 Studies Using Accelerated Titration Design

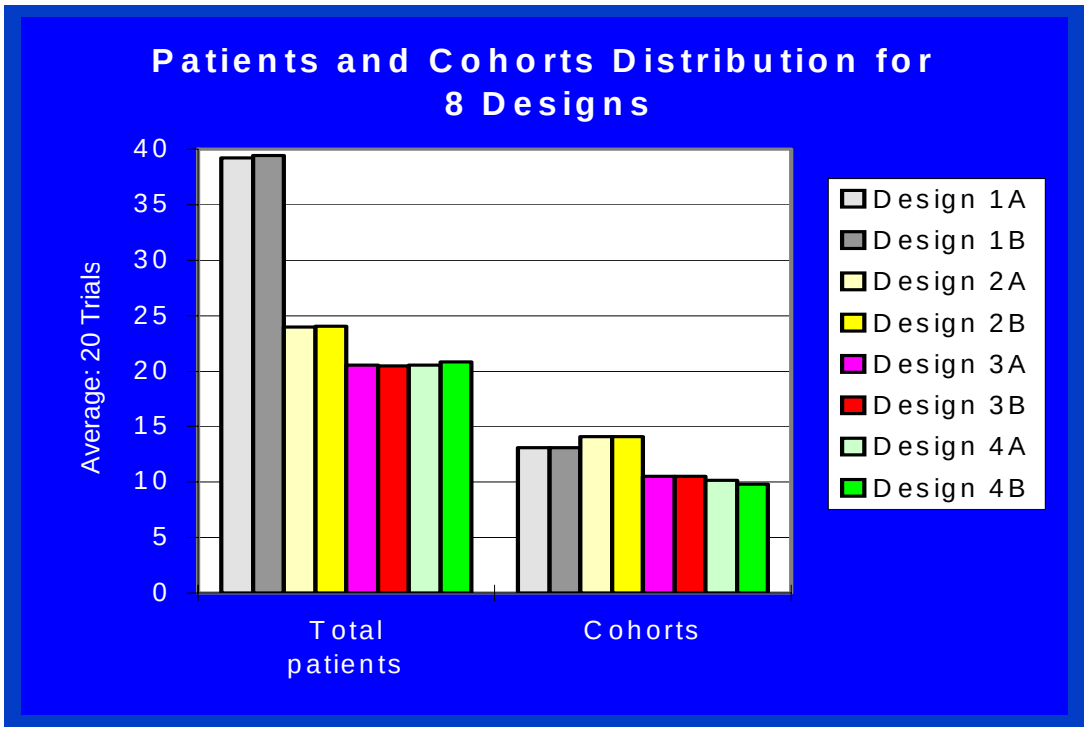

Figure 1: Average Number of Patients and Number of Cohorts for the 8 Designs

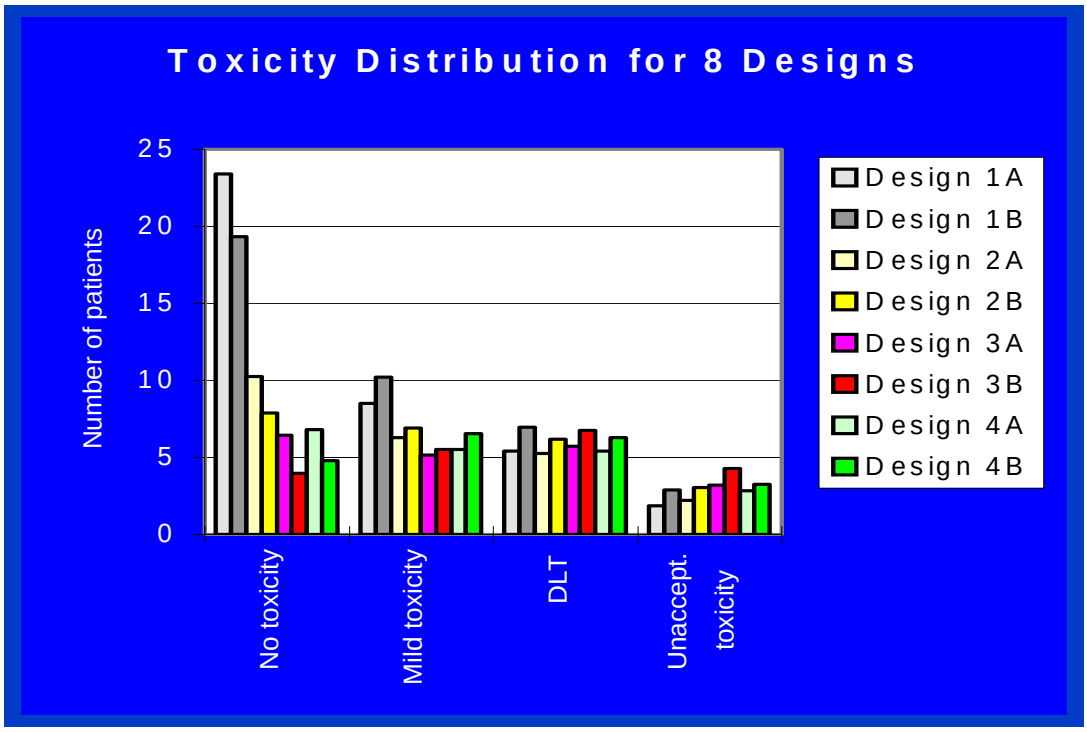

Figure 2: Average Number of Patients with Worst Toxicity at Each Toxicity Level, for the 8 Designs

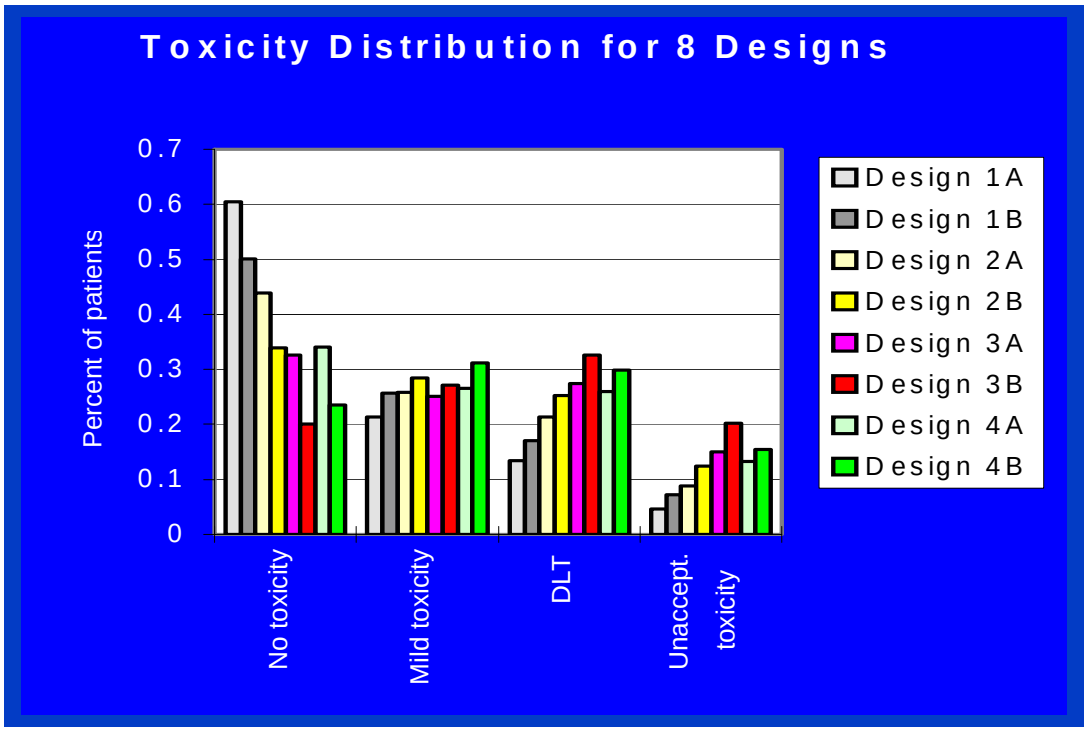

Figure 3: Average Percent of Patients with Worst Toxicity at Each Toxicity Level, for the 8 Designs

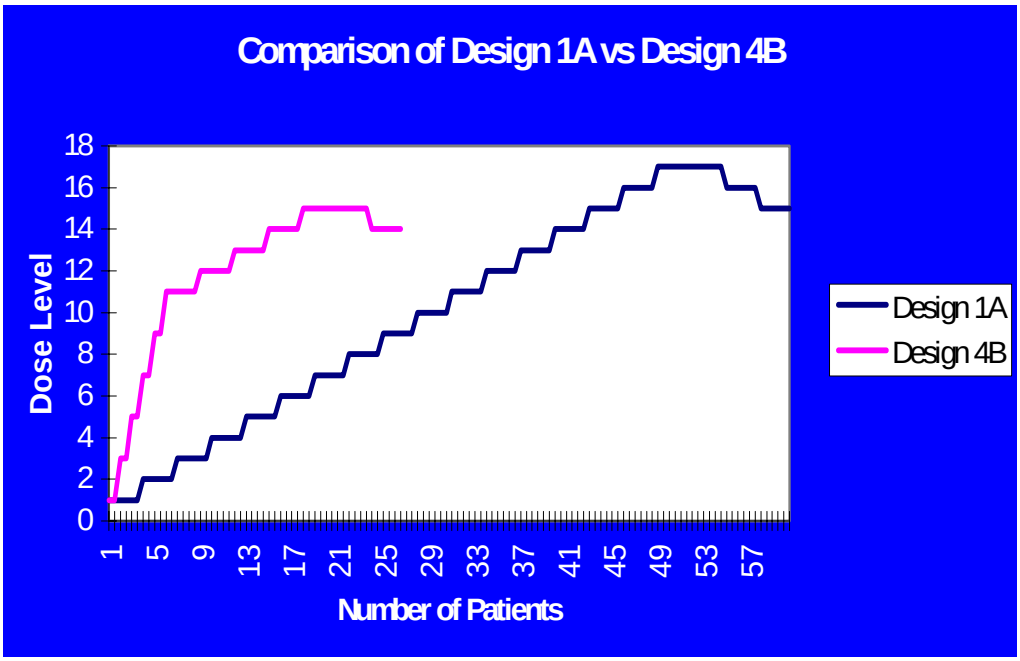

Figure 4: Diagram of the Comparative Performances of Design 1A and Design 4B, in Terms of Patients Required to Reach Each Dose Level and to Define the MTD

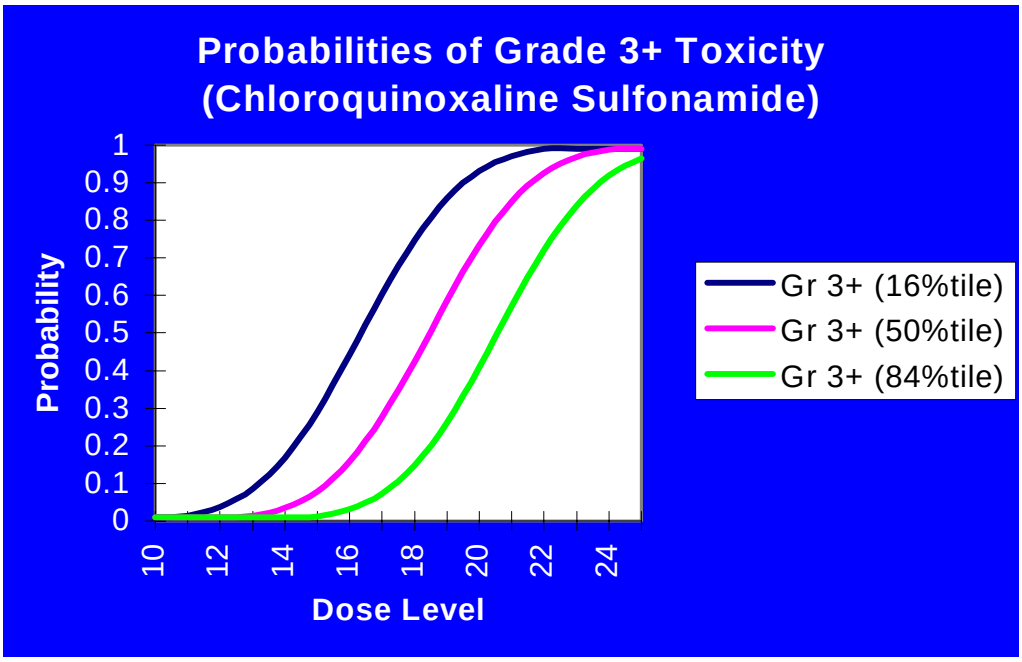

Figure 5: Probabilities of Grade 3+ Toxicity at Various Dose Levels for the Mean Patient and the Patients One STD Above and Below the Mean

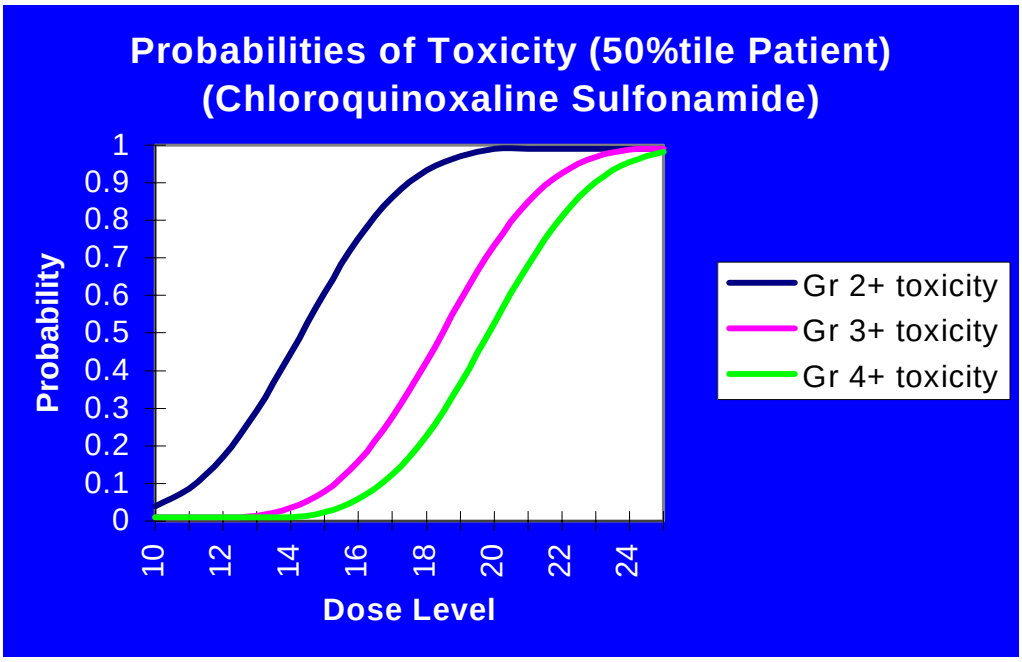

Figure 6: Probabilities of Grade 2+, Grade 3+, and Grade 4+ Toxicity at Various Dose Levels for the Mean Patient