Adaptive designs for dual-agent phase I dose-escalation studies

Jennifer A. Harrington, Graham M. Wheeler, Michael J. Sweeting, Adrian P. Mander and Duncan I. Jodrell

Abstract | Anticancer agents used in combination are fundamental to successful cancer treatment, particularly in a curative setting. For dual-agent phase I trials, the goal is to identify drug doses and schedules for further clinical testing. However, current methods for establishing the recommended phase II dose for agents in combination can fail to fully explore drug interactions. With increasing numbers of anticancer drugs requiring testing, new adaptive model-based trial designs that improve on current practice have been proposed, although uptake has been minimal. We describe the methods available and discuss some of the opportunities and challenges faced in dual-agent phase I trials, as well as giving examples of trials in which adaptive designs have been implemented successfully. Improving the design and execution of phase I trials of drug combinations critically relies on collaboration between the statistical and clinical communities to facilitate the implementation of adaptive, model-based designs.

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Introduction

The effective treatment of cancer frequently requires the use of combinations of drugs because, even if a cancer seems sensitive to one drug initially, cellular heterogeneity can lead to the emergence of drug resistant disease.[1] A combination of drugs can target cancer cells that have differing drug susceptibilities, achieve a higher intensity of dose if the drugs have nonoverlapping toxicities and reduce the likelihood of drug resistance.[2] Indeed, drug combinations have been repeatedly shown to improve survival in patients both with early stage and advanced-stage cancers, and can prove curative even in the metastatic setting, such as in patients with testicular cancer.[3]

The ASCO blueprint for accelerating progress against cancer highlights the need to design "smarter, faster clinical trials, appropriate for the era of molecularly targeted therapies".[4] This need is particularly pressing in the case of early phase trials of combinations of anticancer agents, especially those involving targeted therapies. Increasingly, new agents are developed to recognize a defined molecular target, which offers the opportunity to assess their effect(s) on both the target and the pathway involved. Although information about single-agent toxicity for each individual agent is usually available and can be informative, the pharmacokinetic and pharmacodynamic interactions between multiple agents can considerably influence the dose–toxicity relationships. Consequently, unusual acute and delayed toxicity might occur when drug combinations are administered to patients.[5] These factors necessitate phase I trials that incorporate emerging results of pharmacodynamic end points, whether toxicity-related, biological or efficacy-related, to identify doses or schedules for further evaluation.

Clearly, conducting dual-agent phase I trials for drugs that have already advanced past this clinical stage, albeit individually, is a considerable strain on resources.[6] One strategy that might help address these issues is the use of adaptive clinical trials. The design of these trials is based on using accumulating data to decide how to modify aspects of a study as it continues, without undermining the validity and integrity of the trial.[7] Such adaptation is a design feature and, therefore, any changes are made using a prespecified method rather than on an *ad hoc* basis. Adaptive designs for dual-agent phase I trials have been proposed and evaluated within the statistical literature, with results that suggest their use would facilitate the rapid and effective progression of novel agents to the later phases of clinical development.[8,9] However, few adaptive trials have been used in clinical trials in oncology for reasons that include a lack of familiarity with the methods proposed and concerns of not gaining regulatory approval if using such designs.

Although previous reviews relating to the optimal planning, design and conduct of phase I studies have focused on single-agent studies,[10–12] here we consider the adaptive methods available for dual-agent phase I trials. This Review discusses the potential benefits of novel adaptive trial designs over current methods, examines designs from the published literature and provides examples of their use in oncology practice. We also address the common concerns expressed about the implementation of novel methods for dual-agent phase I trials.

Principles of phase I clinical trials

Phase I trials provide the first assessment of novel drugs or drug combinations with regards to safety, with the

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Key points

- Combination therapy is the mainstay of life-prolonging cancer treatments and increasingly uses both traditional cytotoxic and targeted agents
- Standard rule-based methods for dual-agent clinical trial design have considerable limitations, including slow dose-escalation and that they only consider the outcome of the last cohort to guide escalation
- Adaptive model-based clinical trial designs can be more accurate in recommending combinations to take forward into phase II trials and provide greater flexibility for investigators
- Additional features of model-based designs can be extended to include measurements of chronic toxicity, efficacy, pharmacokinetics and pharmacodynamics, which can be particularly attractive in trials of targeted agents
- Successful examples of model-based designs in practice exist and their further use is strongly encouraged

Box 1 | Understanding the jargon of clinical trials

Dose-limiting toxicity (DLT)
- Medically unacceptable toxic effects that limit dose escalation in a trial

Maximum tolerated dose (MTD)
- In rule-based single-agent trials, the largest dose at which the number of patients with observed DLTs is no greater than a predetermined threshold; for example, at most two patients out of a cohort of six[13]
- In model-based single-agent trials, the dose at which the estimated probability of a DLT occurring in patients is equal to some prespecified target level[13]

Target probability of toxicity (TPT)
- The target probability of DLT associated with the dose that is chosen to be the MTD, typically 20–33% in oncology trials

Assumption of monotonicity
- The core assumption underlying many phase I dose escalation methods that, as the dosage of a drug increases (with all other drugs held constant), the probability of DLTs increases

Recommended phase II dose (RP2D)
- In single-agent trials, the dose of a drug to be recommended for further testing in phase II trials

RP2D contour
- In dual-agent trials, the contour across the dose surface formed by dose combinations that all have a probability of DLT equal to the TPT

RP2D combination
- In dual-agent trials, a dose combination that lies upon the RP2D contour and is to be recommended for phase II trials

Prior probability
- A probability assigned to an unknown quantity of interest before the trial has begun (for example, probability of DLT at specified dose) based on historical data or expert opinion

Posterior probability
- A probability associated with an unknown quantity conditional on its prior probability and other relevant data from the trial associated with it

Bayesian inference
- The combining of current trial data and prior beliefs or probabilities to obtain posterior beliefs or probabilities about quantities of interest

Synergy
- For a given dose combination, the effect (be that efficacious or toxic) of that combination is greater than when the individual effects are added together

Antagonism
- For a given dose combination, the effect (be that efficacious or toxic) of that combination is less than when the individual effects are added together

primary aim of determining the maximum tolerated dose (MTD) and, hence, the recommended phase II dose (RP2D) for efficacy testing. We use the acronym RP2D because the definition of MTD can vary depending on the trial design (Box 1). The toxic effects used to define the RP2D are referred to as dose-limiting toxicities (DLTs),[13] and these are typically reported using binary responses—that is, either a DLT occurs or no DLT occurs. Patients are recruited into a trial sequentially and on the basis of the occurrence of DLTs, subsequent patients receive a dose equal to or higher than the previous patient until the RP2D is defined. The termination of a trial and, therefore, the definition of the RP2D can be governed by specific stopping rules decided on by the investigators or by experimenting on a fixed, finite sample of patients.[14–17] These dose-escalation studies rely on the assumption of monotonicity with respect to toxicity, that is, the probability of observing DLTs increases with increased doses. Many trial designs have been proposed to determine the RP2D.[14,18–22] In dual-agent phase I trials, estimation of an RP2D combination becomes more complex than for single-agent trials. By combining two drugs we now have a 'surface' of dose combinations, whereby the dosage of one or both drugs can be altered, rather than a simple linear dose range. This means that multiple potential RP2D combinations can be defined on the dose surface. These doses form a curve over the dose surface, referred to here as the RP2D contour (Figure 1). Ideally, one or more RP2D combinations should be determined while minimizing the number of patients that receive either subtherapeutic or overly toxic doses.[23]

Two main types of dose-escalation trials have been described: rule-based and model-based. Rule-based designs have set rules that allocate cohorts of patients to one of several predetermined doses based on the DLT responses of the previous cohort. For example, in the commonly used '3 + 3' design, cohorts of three patients are assigned sequentially to increasing dose levels.[14,21] If one DLT is observed in the first three patients, the cohort is expanded by a further three patients. Dose escalation is stopped when two patients (out of the group of three or six patients) given a particular dose, experience a DLT. The design is simple and easy to implement because dose escalation and trial termination are governed by fixed rules. However, there are many issues with the 3 + 3 design that can hinder its usefulness (Box 2).[12,23–26]

By contrast, model-based designs assume a dose–toxicity relationship whereby the probability of a toxicity occurring is characterized by a function of the dose and one or more 'parameters' (a parameter is a number that influences the shape of the dose–toxicity relationship depending on the function chosen).[20] As information accrues during the trial, the dose–toxicity relationship is re-evaluated by updating estimates of the model parameters and subsequent patients are allocated doses that best satisfy chosen decision criteria, which can be, for example, the dose with an estimated probability of DLT closest to the target probability of toxicity (TPT; Box 1). The TPT can be thought of as the permissible proportion of patients that experience some form of DLT.[12]

Many of the models used in these trials are adaptively updated using Bayesian methods, which combine 'prior' information on the dose–toxicity relationship with in-trial data as it is accrued. For each agent, prior

estimates of DLT probabilities are elicited from experts familiar with the preclinical data.[27–30] These estimates can be combined with available historical data to generate probabilities of DLT for each agent when administered alone before the trial is commenced. For dual-agent studies, 'vague' estimates relating to interaction effects are often used because little is known about the synergistic or antagonistic behaviour of the two agents to be examined.[31] However, careful inclusion of preclinical data relating to the interactive behaviour of the agents is recommended to inform—but not dominate—the dose-escalation exercise. Combining this prior information with trial data as it accrues provides an attractive method for adaptive dose allocation to subsequent patients and can aid RP2D contour estimation.

Numerous examples and extensions of model-based designs in the single-agent framework exist.[18,20,22,32] Perhaps the most well-known of these is the continual reassessment method (CRM),[20] a Bayesian adaptive design in which the probability of a patient experiencing a DLT is dependent on the model chosen by the investigators. The CRM requires the dose of the agent (or alternatively a 'skeleton dose', a transformed dose that is a function of the prior probability of DLT at the actual dose given)[33] and a single model parameter (for example, a number that is a power the skeleton dose) as inputs. Given a prior distribution for the parameter—which translates into prior estimates for the probability of DLT for each dose—and previous patients' DLT responses, an updated distribution of the drug's dose–toxicity relationship is obtained (Figure 2) and the next patient is given the dose with an estimated 'posterior' probability of DLT closest to the TPT. This adaptive procedure continues for future patients, adjusting the relationship based on the accrued data. In doing so, both the RP2D estimate and safety assessment can be more accurate than if the traditional 3 + 3 method were used.[20,34] In using a Bayesian method and incorporating relevant prior information, dose-escalation decisions can be better informed than with the 3 + 3 method, allowing fewer patients to be treated at subtherapeutic dose levels. An excellent description of how a dose-escalation trial is conducted using the CRM has been described previously.[35]

Improving aspects of phase I trials

Both rule-based and model-based trial designs can be modified to suit the context of the trial at hand. For example, larger or smaller cohorts can be treated, or escalations to intermediate-dose levels can be conducted. Similarly, pharmacokinetic and pharmacodynamic effects on targets and pathways can be evaluated, which can inform the dosing and schedule.[36,37] Such dose and schedule modifications can be prespecified in the protocol, particularly if an adaptive design is being used; if not prespecified, modifications can be made by amending the trial protocol following a review of data by trial investigators. This flexibility is particularly desirable if, for instance, a succession of DLTs unexpectedly occurs during the trial. An example of this occurring in practice was described in a phase I single-agent trial of

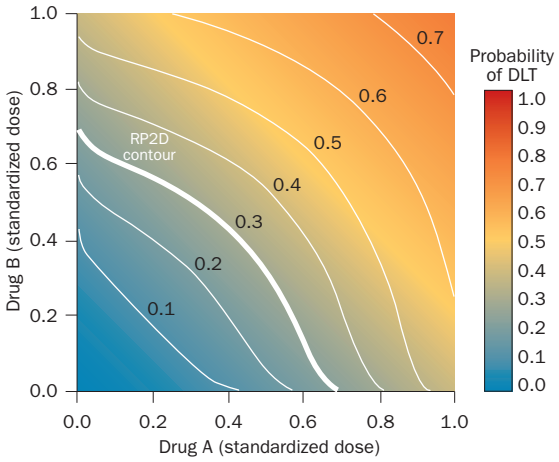

Figure 1 | Example of a 2D dose surface formed by drug A and drug B. The RP2D contour shown for TPT of 0.3 (bold line) is the line of all dose combinations of drug A and drug B that have a probability of DLT equal to 0.3. Using the RP2D contour, investigators can choose any number of dose combinations to be taken forward to phase II trials. Abbreviations: DLT, dose-limiting toxicity; RP2D, recommended phase II dose; TPT, target probability of toxicity.

an unnamed anticancer drug by Neuenschwander *et al.*[38] In the study, the model recommended escalating the dose to 40 mg following the occurrence of two unexpected DLTs in two patients dosed at 25 mg. Trial investigators were able to discuss the findings midtrial and modify the dose choice for the next patient. Consequently, the next patient was treated at 20 mg, after which the model recommended the next eight patients receive the same dose. Of these nine patients, two had DLTs. The trial was stopped and the RP2D was declared as 20 mg.[38]

Another example of design modification is that of the CRM design. Concerns that the original CRM design could expose patients to doses with unacceptably high rates of toxicity led to the introduction of the Modified CRM,[34] which uses slightly more conservative controls on choice of starting dose, number of patients per cohort and the number of dose levels that can be escalated

Box 2 | Common pitfalls of the 3 + 3 design

- The dose escalation is slow because many patients are treated at subtherapeutic doses before the RP2D is identified
- The selected RP2D often has a true probability of toxicity much lower than the commonly believed level of 33%—arising from the fact that the trial stops escalating after observing DLT in at least one-third of patients receiving a dose—and no explicit TPT is set before the trial
- The risk that the RP2D determined using the 3 + 3 design is subtherapeutic is considerable, which can result in subsequent truly effective treatments being abandoned
- The design itself has a 'short memory' in that it only considers the outcome of the last cohort to guide dose escalation

Abbreviations: DLT, dose-limiting toxicity; RP2D, recommended phase II dose; TPT, target probability of toxicity.

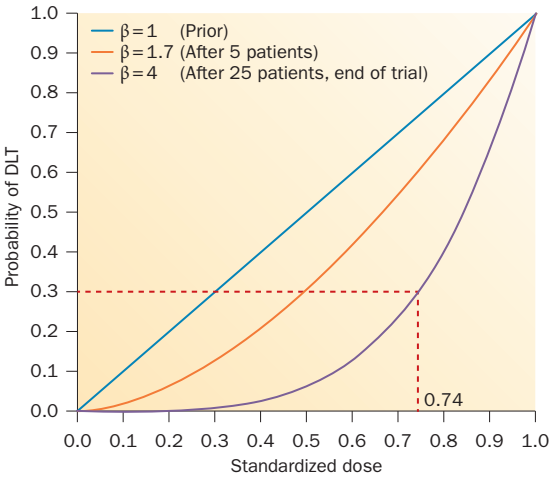

Figure 2 | Mean dose–toxicity relationship for an example trial using the continual reassessment method before the trial begins (blue line), after five patients (orange line) and after 25 patients at the end of the trial (purple line). The dose–toxicity relationship is re-estimated based on the 'prior' estimate (blue line) and incoming data. At the trial's end, the dose with a mean probability of DLT equal to the prespecified TPT of 0.3 is deemed to be 0.74. Abbreviations: DLT, dose-limiting toxicity; TPT, target probability of toxicity.

between cohorts. Further adaptations have included the incorporation of time-to-event (TITE) outcomes, notably the TITE–CRM,[18] which enables investigators to consider delayed toxicity responses to influence dose escalation and schedule decisions, and the work of Braun and colleagues,[39] which directly accounts for the effect of dose and schedule choices on TITE outcomes. Simulation studies have shown the TITE–CRM method to outperform the 3 + 3 method by not only dosing more patients at the true RP2D, but also having shorter trial durations.[40] An example of its application includes the phase I trial of MKC-1 in patients with metastatic solid malignancies.[41] As the target modulation of MKC-1 on the mTOR/AKT pathway was postulated to improve with sustained exposure, the primary objective of the study was to define the MTD (and, therefore, the RP2D) of continuous MKC-1. The researchers felt the modified TITE–CRM algorithm was an optimal method for incorporating toxicity and tolerability, and used the algorithm successfully to assign doses of MKC-1 in the first three patients and in 21 additional patients, taking into account both acute (cycle 1) and late (during cycles 2 or 3) toxicities.

With traditional cytotoxic agents, the prevailing assumption is that the highest tolerable dose is the most effective dose. In addition, the standard indicator of clinical efficacy has been tumour shrinkage, identified using imaging, which is normally measured at periodic intervals well after cycle 1 toxicity assessments. As eligible patients in phase I oncology trials generally have advanced refractory disease with progressive disease after only a few cycles of treatment, antitumour activity data has not been widely incorporated into decisions about dose escalation. Past reviews have highlighted that toxicity end points alone are still used to define RP2Ds in the majority of phase I trials.[12,42] However, with targeted agents this hypothesis might be invalid because such agents can be cytostatic and not lead to tumour shrinkage. Furthermore, surrogate measures of clinical efficacy, such as markers of target modulation or pharmacokinetic end points, can now be reported rapidly and the results made available to researchers prior to making the next dose-escalation decision. In this context, an ideal model would recommend RP2D combinations based on both toxicity and markers of target modulation,[43,44] which should minimize toxicity that can occur with off-target effects at higher concentrations of the drug.[12,45]

Another important design consideration is whether additional detailed information about toxicity can be incorporated into dose-escalation decisions. The majority of trial designs use binary responses for each outcome (for example, DLT or no DLT), but toxic reactions are graded according to severity on a scale between 0 (no toxicity) and 5 (death).[46] Thus, an ordinal scale—or a continuous response variable—would be more appropriate because the observation of low-grade toxic reactions can be used to indicate whether high-grade or severe toxic reactions at increased dose combinations are likely. Using a continuous scale is of particular interest in trials of targeted agents, (which are frequently administered continuously) and trials that permit intrapatient dose escalation in which multiple low-grade toxicities over time and treatment cycles can have greater negative effects on a patient than single grade 3 or 4 toxic events during cycle 1. Incorporating toxicity grading (and how it relates to the dose schedule) can help make optimal dose and schedule choices. For model-based designs, methods have been reported that incorporate ordinal and continuous response variables by, for example, converting graded toxicity information into numerical scores,[47,48] and by considering cumulative toxicity over a number of treatment cycles in which intrapatient dose escalation and schedule changes are permitted.[49] With these adaptations, increasingly detailed information per patient is available and the chances of placing patients on doses or schedules that are dangerously toxic are reduced.[50,51] Concurrently, the extra information can lead to increasingly accurate estimations of the RP2D contour[47] and—in trials concerned with antitumour activity end points—more-accurate estimations of the therapeutic window.

Within dual-agent trials in which toxicity is the only outcome, consideration is required as to whether a single RP2D combination or multiple RP2D combinations are to be identified. With respect to toxicity, any of the dose combinations on the RP2D contour could be taken forward into phase II testing. The current approach is to choose not to evaluate multiple doses or schedules because of practical concerns (regarding time, cost and the additional patients required) together with the pragmatic view that one dose or schedule is preferred. However, more than one RP2D combination might be equally effective at inhibiting the target, and these combinations could then be compared in a randomized phase II trial for efficacy. Ideally, the selection of dose combinations from the RP2D

contour should be combined with an evaluation of anti-tumour effect to facilitate the choice of combination(s). By not fully exploring the surface of dose combinations formed by the two drugs being investigated, a trial might overlook the most efficacious dose combinations or dose combinations with reduced toxicity.[52] In our opinion, this possibility is an important consideration for future trials involving targeted agents.

Overall, model-based designs are better equipped to provide a statistical framework for the incorporation of additional data (both prior and accrued) into dosing and schedule decisions that rule-based designs—in particular, the 3 + 3 method—often lack. The benefits of model-based designs compared with the 3 + 3 design and other rule-based methods have been reviewed,[12,19,20,53–56] yet their implementation in clinical practice is infrequent. Indeed, a review of all phase I cancer trials published between 1991 and 2006 showed that <2% used Bayesian adaptive designs,[54] and a subsequent update showed very few model-based designs are in clinical use for a variety of reasons that will be explored later in this Review.[12]

Dual-agent phase I trial designs

The standard method

Currently, many dual-agent trials fix the level of one drug either at its single-agent RP2D or at a dose close to it (normally the drug with the most prior information). The other agent is then escalated, with the initial aim of reaching its single-agent RP2D dose, although this dose is often limited by the occurrence of DLTs. This method is based on the assumption that if the agents to be administered in combination have different mechanisms of action or nonoverlapping toxicities, reaching the RP2D of each single agent would be the optimal drug combination.[12] Typically, the single-agent 3 + 3 design is used for dose escalation of the nonfixed agent in the combination and, hence, only a limited number of dose levels are explored (Figure 3a). Any reductions in either agent's dose because of tolerability issues are regarded as compromises, with decisions made on the basis of multiple factors, including ethical, regulatory, safety and scientific concerns.

A problem with this standard approach is that the fixed-dose agent is already one that can cause considerable toxicity and, therefore, assessing the tolerability of an additional and presumably toxic drug is challenging. Unless a pharmacodynamic readout is available, the occurrence of a DLT can halt the escalation of the second drug and lead to suboptimal target inhibition. This eventuality is particularly pertinent given the small numbers of patients typically included in a dose cohort study and in the oncology population (where patients are often heavily pretreated before being enrolled in phase I studies). That is, these patients are by definition more susceptible to additional toxicity than the patients who will eventually be treated with the drug. An alternative method (Figure 3b) could enable a much wider range of combinations to be tested.

Rule-based modifications

Alternative rule-based designs incorporate modifications to the standard dual-agent trial design to examine a much wider range of combinations. Different strategies for dose escalation that have been explored include alternate escalation of the agents in the series of dose levels, simultaneous escalation of both agents and performing two trials using the standard method, holding different agents constant for each trial.

The '3 + 3 + 3' method[57] applies the first two of these strategies. The method explores a rectangular grid of drug combinations (Figure 4), initially by sequentially dosing cohorts of three patients along the diagonal of the dose combination grid either by the alternate escalation of each agent per cohort or by escalation of both agents simultaneously. The rules for escalation, de-escalation and trial termination are governed by six 'tuning' constants that are determined by the researchers before the trial starts. These constants are thresholds that relate to the number of observed DLTs in a cohort. Once a prespecified number of patients in the most recent

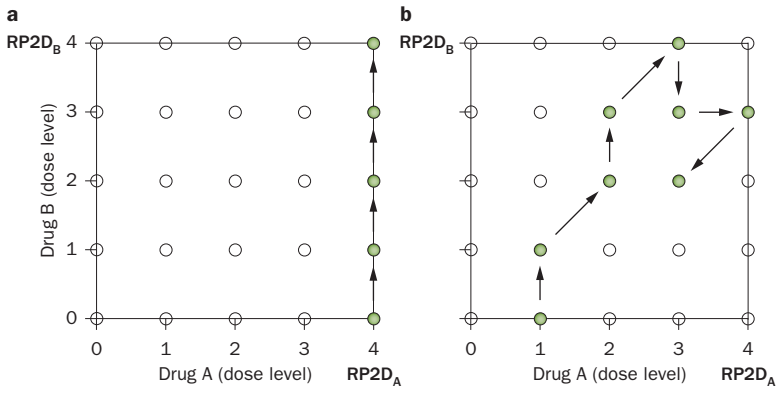

Figure 3 | Examples of dose-escalation studies using **a** | standard method of dose escalation, with drug A fixed at its RP2D when administered alone (RP2D$_A$), and **b** | exploration of full dose surface to find possible RP2D combinations. Abbreviation: RP2D, recommended phase II dose.

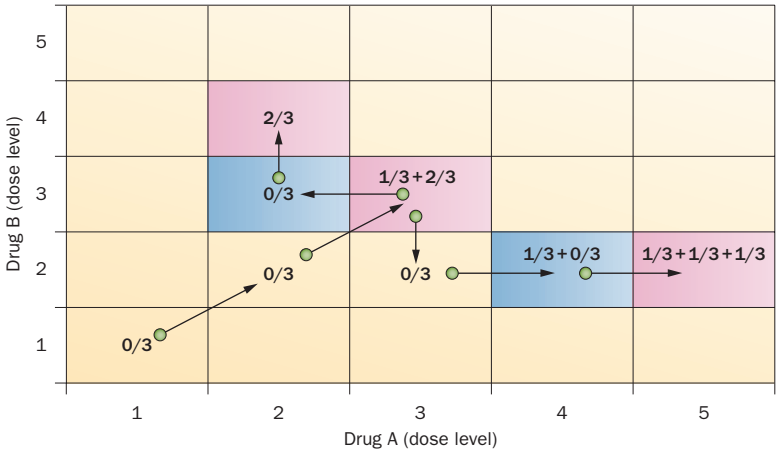

Figure 4 | Example of a 3+3+3 escalation study. Arrows indicate dose-escalation pathways. Pink cells indicate dose combinations with unacceptably high DLT rates. Blue cells indicate final RP2D combination selections. A cell denoted '1/3' indicates that 1 patient out of 3 experienced a DLT. Different cohorts are separated by '+'. When a prespecified number of patients in the latest cohort experience an unacceptable number of DLTs, the trial splits into two separate searches, with cohorts of three patients each given increasing doses of one of the drugs. Abbreviations: DLT, dose-limiting toxicity; RP2D, recommended phase II dose.

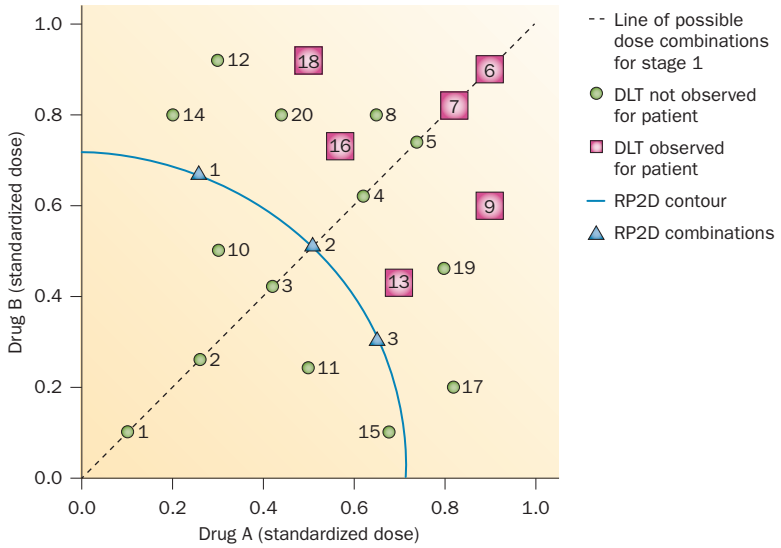

Figure 5 | Selection of three RP2D combinations based on an example trial using a known model.[31] Initial escalation occurs along the diagonal (dashed) line. Following this, patients are dosed over the dose surface along the best estimate of the RP2D contour. Numbered points denote the patient identity (green circle implies patient did not experience DLT; red square implies patient experienced DLT). At the end of the trial, the final RP2D contour (blue line) is estimated by the model and three RP2D combinations are selected (blue triangles). Abbreviations: DLT, dose-limiting toxicity; RP2D, recommended phase II dose.

cohort experience an unacceptable number of DLTs, the trial splits into two separate searches off the diagonal of the dose grid, with cohorts of three patients each assigned to escalation of one of the drugs. This flexibility provides the trial the ability to be more or less conservative depending on the agents used, patient population, disease and the type of DLTs expected.

Lee and Fan[58] proposed an extension to these designs, using information on agent-specific DLTs (non-overlapping toxicities) to help guide escalation. The 3 + 3 + 3 design can be generalized to incorporate differently sized cohorts, referred to as 'A + B + C' designs, whereby A, B and C are numbers corresponding to cohort sizes used in the trial.[26] However, according to the rules that govern the A + B + C design, only a maximum of two RP2D combinations can be selected.

In a third method, Lee *et al.*[59] implemented a two-stage design for a phase I trial of combined cisplatin and 9-nitrocamptothecin therapy. In the first stage, the standard method was applied twice: once with the cisplatin dose held constant and once with the 9-nitrocamptothecin dose held constant. For the second stage, the probability model of Thall *et al.*[31] was fitted to the first-stage data. The model was not used to govern dose escalation, but was used to obtain estimates for the probability of toxicity per dose combination, from which a single RP2D combination was determined.

Although these designs aim to improve upon the standard method, several limitations remain (Box 2). Additionally, the lack of an explicit TPT means that detailed simulation studies of various designs must be explored to fully understand their operating characteristics, such as the percentage of simulated trials that recommend the 'correct' RP2D combination and percentage of patients that receive severe underdoses or overdoses. Thus, the probabilities of DLT associated with the selected RP2D combinations might be well below—or indeed above—values deemed acceptable.[26]

Model-based modifications

The importance of prior information to model-based phase I trial designs has led to several proposals for these trials to consist of two parts. In this way, a start-up stage obtains preliminary data that can be fed into the statistical model, often via a simple rule-based escalation procedure that ceases when a patient exhibits a DLT. Once completed, the second stage implements the model-based part of the methodology.[60–64] For example, Wang and Ivanova[60] proposed a two-stage design that uses an initial rule-based stage, before switching to a model-based stage to dose the next patient at the best estimate of the RP2D combination. Indeed, one model-based design,[63] which implemented a rule-based start-up stage, has been used in a seamless phase I–II clinical trial of decitabine and a derivative of recombinant interferon in patients with metastatic melanoma, with adaptive randomization used after dose escalation to determine the most efficacious dose combinations.[65] After 20 patients had been recruited to the phase I study, three RP2D combinations were taken forward to phase II testing.

By contrast, Thall *et al.*[31] propose an entirely model-based two-stage dual-agent dose-escalation design. The model for the probability of DLT has six parameters—four of which describe the probability of toxicity at the margins (that is, when each drug is used as a single agent) and the remaining two parameters model the interactive behaviour of the agents when combined. The first stage implements a Bayesian CRM to sequentially recommend dose combinations along a fixed diagonal line on the dose surface to several patients. After these patients have had their DLT responses recorded, the second stage allocates the next patients to dose combinations along the estimated RP2D contour, which is determined based on the data from the first stage. The model recommends three RP2D combinations at the end of the trial from the final RP2D contour; one from the diagonal line across the dose surface, one dose combination on the estimated RP2D contour that lies above the diagonal and one on the estimated RP2D contour below the diagonal (Figure 5). Simulation studies for multiple dose–toxicity scenarios have been conducted in an example trial of gemcitabine and cyclophosphamide, showing that a trial size of 50–60 patients provides reliable and accurate estimates of RP2D combinations.[19,32] A stand-alone software program (ToxFinder) from the MD Anderson Cancer Center, Houston, TX, is available to run extensive simulation studies using this model and can be downloaded online.[66]

An alternative design uses a logistic regression model to calculate the probability of DLTs, given the dose level of the first drug and a set of indicator variables that specify whether the dose level of the second drug is above various thresholds—for example, one variable takes a value of 1 in the regression model if the second

drug exceeds 400 mg/m^2 (and 0 otherwise), whereas an additional variable takes a value of 1 if the second drug exceeds 600 mg/m^2 (and 0 otherwise).[67] This approach was used to investigate the combination of nilotinib and imatinib in patients with imatinib-resistant gastrointestinal stromal tumours. Of the 53 patients that were enrolled in the trial, nine experienced DLTs. At the end of the trial, three dose combinations with mean posterior probabilities closest to the predefined TPT of 20% were identified. From these combinations—following a consultation with the clinical trial team—an RP2D combination of nilotinib 800 mg and imatinib 400 mg daily was selected to go forward into phase II trials.[67]

Ordering combinations based on toxicity

Understanding the true dose–toxicity relationship of all combinations is a complex issue faced in dual-agent dose-escalation studies. As illustrated in Figure 6, although the assumption of monotonicity states that dose combinations B and C are more toxic than combination A, we do not know whether dose combination B is more toxic than C or vice versa. Thus, we say that the dose–toxicity relationship for these two agents in combination is only partially ordered. By contrast, a simple order is one in which we are able to definitively state which doses are more or less toxic than others for all dose combinations to be studied. Under a known partial ordering of dose combinations, multiple simple orders exist. By selecting a simple order of dose combinations from the known partial order at each dose-escalation stage, we can reduce a complex 2D escalation problem to one dimension. In Figure 6, two possible simple orders arise from the known partial order: either C is more toxic than B, which is more toxic than A, or B is more toxic than C, which is more toxic than A. By reducing the dimensionality of the dose-escalation problem, we can apply existing, well-studied single-agent dose-escalation methods (such as the aforementioned CRM) to conduct the trial.

Two models have been reported that exploit the simple ordering of doses from a partial order. We believe these are appealing for clinical practice because one can still explore the surface of dose combinations and incorporate current trial data, but the dose-escalation decision for the next patient is far simpler. Conaway *et al.*[68] use current trial data to obtain weighted averages—over all simple orders resulting from the known partial order—of the probability of DLT at each dose combination and choose the combination that has a probability of DLT closest to the TPT. By contrast, Wages *et al.*[69,70] 'weight' each possible simple order at each stage of the trial and select the order with the highest weighting to determine the next dose-escalation step.

In summary, various modifications to the standard method of dose escalation in dual-agent phase I clinical trials have been proposed. These include different rule-based methods, such as permitting the alternate escalation of agents to increase the flexibility of the design. Others have recommended using an initial start-up rule-based escalation and then switching to a model-based stage. However, entirely model-based designs now also exist, and have started to be used in clinical practice, albeit sparingly.

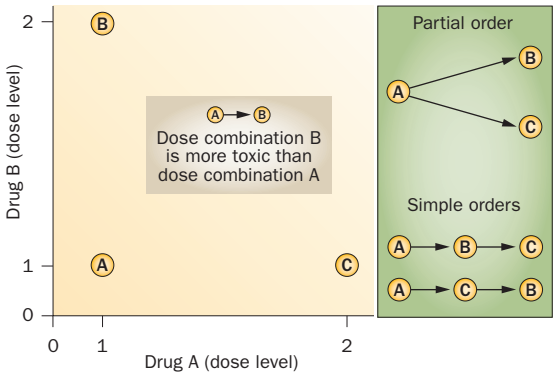

Figure 6 | Illustration of a simple dose combination grid, showing all possible simple orders that satisfy the known partial ordering of dose combinations with respect to toxicity. By assuming a simple order, explicit statements about the dose–toxicity relationship of different combinations can be made and the complexity of the dose-escalation decision process is reduced.

Designs for efficacy and toxicity

Although the potential advantages of considering both markers of target modulation or antitumour activity and toxicity in a phase I trial have been discussed earlier, phase I trials rarely incorporate such information, partly because of the issues described. However, various designs have been proposed to include this assessment in phase I dose-escalation studies.

Rule-based designs

Huang *et al.*[71] propose a seamless phase I/II trial design that initially considers the toxicity of dose combinations, followed by assessing the efficacy of a subset of dose combinations chosen from the first stage. For dose escalation, a modified 3 + 3 design is implemented, whereby escalation is further constrained by whether doses in the same 'zone'—defined by the assumption of monotonicity—have been successfully experimented with or not (Figure 7). This first stage reduces the set of dose combinations to a smaller set of admissible doses, which can then be examined for antitumour activity or target modulation using adaptive randomization. Biswas *et al.*[72] applied a similar method to a phase I/II combination trial of 5-azacytidine and Ara-C (cytarabine). In the study, 34 patients with relapsed or refractory acute myeloid leukaemia or high-risk myelodysplastic syndrome were studied across four dose combinations and, of these, two patients experienced complete remission.[72]

Model-based designs

Mandrekar *et al.*[73] describe a Bayesian model in which three probabilities are modelled: the probability of no response (no efficacy and no toxicity), the probability of success (efficacy and no toxicity) and the probability of toxicity (toxicity regardless of efficacy). Using prior estimates for the model parameters and toxicity and efficacy data from patients, a recommended dose combination for the next patient is selected. This model was originally proposed as a model for single-agent trials.[74] Results from

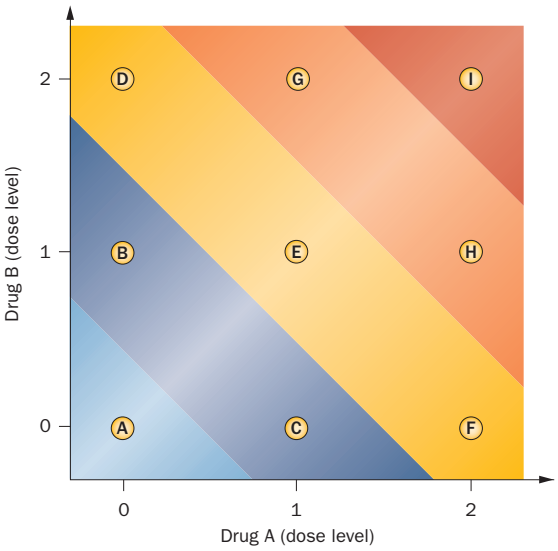

Figure 7 | Dose grid and zones.[71] Dose combinations B and C are more toxic than dose A. However, whether dose B is more toxic than dose C is unknown, so they are allocated to the same 'zone'. Escalation from dose B to any dose in the next highest zone (with combinations D, E and F) can only occur if dose C has been successfully experimented with previously as well as dose B. Otherwise, the next cohort of patients is assigned to dose C. Permission obtained from John Wiley and Sons © Huang, X. *et al. Biometrics* **63**, 429–436 (2007).

simulation studies with a maximum sample size of 45 patients with 15 dose combinations indicate this method provides fairly reliable estimations of RP2D combinations over a variety of dose–toxicity and dose–efficacy relationships, in terms of number of patients receiving overly toxic doses and the percentage of trials that recommend the true RP2D combinations.[44,73]

Whitehead *et al.*[75] use these three probabilities, but can also distinguish between the probability of toxicity and efficacy and the probability of toxicity and no efficacy. These four probabilities (referred to as 'risks') can only take one of a set of discrete values. For example, the set of values can be 0.1, 0.3, 0.5 and 0.7, or perhaps 0.2, 0.4, 0.6 and 0.8. On the basis of the core assumption of monotonicity—applied to both dose–toxicity and dose–efficacy relationships—for each dose combination, the model updates the probability that the risk of a particular event is equal to each of the discrete values. This method provides an illustration of the toxicity–efficacy trade-off yielded when the two agents are combined, therefore, informing clinicians which dose combinations should be carried through to phase II. Indeed, this design is currently being used in a combination phase I trial of gemcitabine and MK-0752 in patients with pancreatic cancer.[76] The trial has been adapted to include 'accelerated implementation', whereby dose allocation can be made before waiting for the previous patient to complete the 6-week treatment cycle. This modification is likely to reduce the length of the trial and only increase the planned sample size by a nominal amount.

In addition to these examples, increasingly complex models have been proposed. For example, Houede *et al.*[77] propose the use of a model in which both efficacy and toxicity are modelled as ordinal responses. A stand-alone software program called U2OET is available from MD Anderson Cancer Center.[78] By constrast, Dragalin *et al.*[79] discuss models with binary, ordinal or continuous patient responses for efficacy and toxicity. Both of these designs provide more-realistic outcomes for dual-agent phase I trials than those with binary responses, since more information about the dose–toxicity relationship of the combinations can be obtained and adaptively used. Furthermore, these designs are mathematically tractable and possess inherent flexibility.

Deciding which trial design to use

Valuable insights into the operating characteristics of each design under different dose–toxicity scenarios can be gained from comparative simulation studies. Furthermore, such comparisons can provide an understanding of the design behaviour when used in clinical practice. Several simulation studies in the literature have compared novel trial designs to either the standard method[61] or other model-based designs.[8,70,80] In addition, a theoretical comparison has been reported of several model-based dual-agent phase I designs in terms of risk-ratio functions, which help illustrate whether particular models can capture synergistic or antagonistic toxicity behaviour.[81] These comparisons suggest that Bayesian model-based designs are preferable to the standard method, because prior information and all data accrued during the trial can easily be combined to aid the dose-escalation decision making process and better estimate the underlying dose–toxicity or dose–efficacy relationships.[12,67,80,82] Similar to single-agent comparative studies, more patients are likely to be dosed at or close to the true RP2D combinations in trials with the Bayesian model-based design.[19,55,56,61] However, a fair comparison is difficult to achieve because Bayesian adaptive model-based designs incorporate prior information, whereas rule-based designs do not. Indeed, an in-depth sensitivity analysis of the effect of prior information on trial performance is required. To provide a reference point for future comparisons, each design's main features, including the responses they measure, the number of parameters required and the number of RP2D combinations provided must be considered (Table 1).

Furthermore, no thorough comparison of the novel model-based methods and their novel rule-based counterparts has been reported for dual-agent dose-escalation studies. As many of the methods discussed here are relatively new (published between 2007 and 2012), this is perhaps unsurprising. Importantly, the relative adolescence of such designs—and, accordingly, their rarity in clinical practice—means that we are unable to obtain details on subsequent phase II and phase III trials of combinations of agents that have been evaluated from the phase I designs.

When deciding to implement a particular dual-agent phase I design, several important factors must be considered. First and foremost, one must consider the quantity and quality of the preclinical and clinical information available for each drug. It might be the case

Table 1 | Summary of features for various dual-agent dose escalation study designs

Study	Number of model parameters	Stages	Outcomes	Response values	Number of RP2D combinations
Rule-based designs					
Hamberg and Verweij (2009)[57]	–	1	Toxicity	Binary	1 or 2
Lee and Fan (2012)[58]	–	1	Toxicity	Binary	1 or 2
Huang *et al.* (2007)[71]	–	2	Toxicity and efficacy	Binary	0 or 1
Lee *et al.* (2008)[59]	–	2	Toxicity	Binary	1
Model-based designs					
Wang and Ivanova (2005)[60]	3	2	Toxicity	Binary	Minimum number of doses of drug A or drug B
Yin and Yuan (2009)[62]	3	2	Toxicity	Binary	1
Yin and Yuan (2009)[63]	3	2	Toxicity	Binary	1
Kramar *et al.* (1999)[61]	2	2	Toxicity	Binary	1
Su (2010)[64]	1	3	Toxicity	Binary	1
Thall *et al.* (2003)[31]	6	2	Toxicity	Binary	3
Mandrekar *et al.* (2007)[73]	6	1	Toxicity and efficacy	Binary (toxicity and efficacy)	1
Houede *et al.* (2010)[77]	21	1	Toxicity and efficacy	Ordinal (toxicity and efficacy)	1
Dragalin *et al.* (2008)[79]	8	2	Toxicity and efficacy	Binary, ordinal or continuous (toxicity and efficacy)	1
Whitehead *et al.* (2011)[75]	Between K and $3K$*	1	Toxicity and efficacy	Binary (toxicity and efficacy)	Trial dependent (0–9)
Conaway *et al.* (2004)[68]	K	2	Toxicity	Binary	1
Wages *et al.* (2011)[70]	M‡	2	Toxicity	Binary	1
Wages *et al.* (2011)[69]	M‡	1	Toxicity	Binary	1
Braun and Wang (2010)[80]	6	1	Toxicity	Binary	1
Bailey *et al.* (2009)[67]	≥3§	1	Toxicity	Binary	1

*Number of parameters depends on the choice of discrete values that 'risks' can take. ‡(M – 1) parameters for weights on simple orders, plus one parameter for the dose-escalation model. §Two parameters required for drug A, plus one or more parameters for number of indicator variables for drug B. Abbreviations: K, number of combinations; M, number of simple orders; RP2D, recommended phase II dose.

that the two drugs are each already well-established chemotherapeutic agents, or that only preclinical information is available for one or both drugs. As FDA guidelines on the co-development of drugs for use in combinations requests investigators have suitable information on both agents,[83] investigators might feel that a two-stage design, with an initial gradual escalation stage, is suitable for studies that include agents with little pharmacokinetic or pharmacodynamic data.

One must also consider what the outcomes of interest are and how they are to be measured. Are we only interested in toxicity responses or efficacy measures as well? Will binary outcome variables suffice, or should toxicity grading or continuous measurements be incorporated? Should outcomes be time-to-event variables? Answering these questions will reduce the number of appropriate designs to a manageable level. Another major consideration—particularly when considering a model-based design—is the statistical expertise available. The presence and input of statistical experts from the design stage through to the trial's inception and conclusion is required for dual-agent phase I studies. Several institutions are actively implementing and developing novel model-based adaptive designs, most notably the University of Texas MD Anderson Cancer Center, Novartis Pharma AG (Basel, Switzerland), the Medical and Pharmaceutical Statistics Research Unit at Lancaster University (UK), the Medical Research Council Biostatistics Unit Hub for Trials Methodology Research (UK) and Cancer Research UK. Furthermore, easy-to-use stand-alone software packages are freely available to download from several institutions and organizations.[84–86]

One also needs to be aware of the available patient population, whether the trial is to be restricted to patients with specific tumour types, according to the presence of particular biomarkers or whether patients with multiple tumours in different sites can be enrolled. Additionally, by escalating both agents and exploring the

Table 2 | Completed dual-agent phase I trials using novel adaptive designs

Method	Agents combined	Number of dose combinations	*n*	Number of RP2D combinations
Lee *et al.* (2008)[59]	Cisplatin and 9-nitrocamptothecin	12	54	1
Huang *et al.* (2007)[71]	5-Azacytidine and Ara-C	4	34	4
Whitehead *et al.* (2012)[76]	Gemcitabine and MK-0752	10*	60‡	Still recruiting
Yuan and Yin (2011)[65]	Decitabine and recombinant interferon derivative	6	20	3
Bailey *et al.* (2009)[67]	Nilotinib and imatinib	5	53§	1

*As per Whitehead *et al.*[76] ‡Estimated. §Three patients subsequently removed from dose-determining set due to protocol deviations. Abbreviation: RP2D, recommended phase II dose.

surface of dose combinations, many dual-agent dose-escalation designs might require more patients than the standard trial design, which requires the number of available patients to be no more than six times the number of dose combinations considered. However, the use of more patients over the entire surface of dose combinations means investigators gain more information about the combination therapy; depending on the trial aims and outcomes used, the efficacy–toxicity trade-off of both agents can be better evaluated and multiple RP2Ds can be chosen (Table 2).

Given these factors and considerations, recommending a single 'gold-standard' design for dual-agent phase I trials is not currently possible. Indeed, the choice of probability model, dose-escalation decisions, the starting dose combination and how the outcomes are recorded are best determined by thorough and informed discussions between investigators and trial statisticians.[32] Such collaboration will provide a trial design that is complex enough to measure and model the outcomes of interest and address the underlying aims, but also consider ethical and regulatory issues. The models discussed in this Review are all consequences of such discussions and their flexible nature enables further modifications to best suit any particular trial set-up.

Increasing novel design implementation

Both the FDA[87] and European Medicines Agency (EMA)[88] have recommended the use of novel trial designs, particularly those using prior experience or accumulated information in the design. That Bayesian adaptive designs have not been implemented widely in oncology has prompted discussion of whether Bayesian adaptive clinical trials—including and beyond phase I—are only of interest to the statistical community.[89] Bailey *et al.*[67] noted that a major concern with Bayesian model-based designs "… has been the acceptance and support that could be expected from clinical colleagues, investigators and regulatory agencies alike". Mandrekar *et al.*[44] similarly list pragmatic issues relating to the minimal use of model-based designs that includes a lack of familiarity with the novel methods proposed, an unfounded fear that using a model to recommend dose escalations removes control from investigators, and concern of not gaining regulatory approval if using such designs. However, Bailey *et al.*[67] state that a close working relationship between the trial statisticians and study clinicians, plus nontechnical training on Bayesian inference and data interpretation, enabled all parties involved in the dose-escalation decision-making process to be fully informed and comfortable with the new methods. Furthermore, the use of adaptive designs provided investigators and the clinical trial team with a better command of trial progress; dose escalation can be guided by a model's formal recommendations, but investigators are able to discuss or override these if necessary.

This method of clinical trial design is, of course, in contrast to a reliance on a predefined algorithmic approach. As for regulatory approval, ASCO, the FDA and EMA have each introduced guidance to encourage the use of Bayesian adaptive designs in oncology.[90,91] An Institute of Medicine workshop on facilitating collaborations to develop combination investigational cancer therapies also acknowledged the benefit of Bayesian adaptive trial designs,[92] mentioning the FDA's revision of guidelines on co-development of two or more novel agents to be used in combination.[83] Such resources, along with user-friendly software libraries, support the need to improve how dual-agent phase I trials are conducted. With mounting evidence in favour of such designs over the standard method that is used in the majority of trials, neglecting these efficient adaptive designs seems illogical.

Gönen has identified three barriers to the use of Bayesian clinical trials: prior information, software and motivation.[93] Although careful consideration and work is required to construct prior distributions, methodologies to construct appropriate prior distributions via expert elicitation are widely available for dose-escalation studies.[27,28,30] Furthermore, conducting pretrial simulation studies to examine how elicited prior estimations affect dose-escalation behaviour is easily achievable and 'design priors' can be used to emulate the desired behaviour of the escalation process. For example, if upon review of simulation studies, a panel of clinicians is wary of how quickly a particular design escalates, they can discuss this with the statistician and suggest alterations. The priors can then be adjusted and further simulation studies conducted until the clinicians are comfortable with the model behaviour. With respect to software, we are now in a position to implement advanced computational methods to conduct vast simulation studies to summarize a model's operating characteristics. Improved infrastructure and technology can ensure rapid transfer of patient data, including real-time pharmacokinetic and pharmacodynamic data, enabling models to be updated continuously during a trial. From a motivational perspective, the potential superiority of adaptive designs in this era of drug development—whereby multiple additional acute and chronic toxicity, pharmacokinetic and pharmacodynamic end points can be used—advocate the greater use of these newer designs. Furthermore, these designs address the considerable challenges of combination drug studies, which should go some way to promoting their increased use.

Conclusions

A variety of designs are now available for phase I trials of drug combinations. The main characteristics of rule-based designs are that they do not incorporate any prior information, and have limited flexibility in the light of emerging toxicity data. Simulation studies have revealed that model-based designs are more likely to treat a higher number of patients closer to optimal dose levels than rule-based designs because they incorporate prior information and use all the available trial data in making dose-escalation decisions.

The clinical oncology community has been particularly reluctant to consider using these model-based designs, despite statistical expertise and resources being readily available. Only through their use will the true value of model-based trials begin to improve drug development. Although the standard dual-agent method can provide the reassurance that patients are at least receiving one drug at its full dose (and, therefore, gaining potential benefit from enrolling in the trial), a model-based design exploring the entire dose surface might require a lower starting dose than used in practice of an established drug. However, only model-based designs offer the flexibility to identify true synergistic activity with respect to antitumour activity and to identify less-toxic combinations. Given a truly collaborative spirit between informed clinicians and statisticians, these trial designs will assist in the optimal development of exciting new drug combinations, changing the way we treat patients with cancer and improving their outcomes.

Review criteria

An initial search was conducted using the PubMed database for articles published in English before 24 June 2012 using the search terms "clinical trial design", "Bayesian trial design" and "phase I". The papers identified were then individually searched to identify those relevant to dual-agent design. The search was updated on 18 December 2012 following peer review. In addition to this, the authors searched their own files for relevant publications and followed up citations in seminal statistical papers.

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