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Current perspective

Dose-escalation models for combination phase I trials in oncology

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ABSTRACT

Designing combination drug phase I trials has become increasingly complex, due to the increasing diversity in classes of agents, mechanisms of action, safety profiles and drug-administration schedules. With approximately 850 agents currently in development for cancer treatment, it is evident that combination development must be prioritised, as based on a specific hypothesis, as well as a projected development path for the involved combination.

In this manuscript the most relevant issues and pitfalls for combination drug phase I trial design are discussed. Several phase I study designs that incorporate controls to circumvent bias due to imbalances in observed background toxicity are discussed.

1. Introduction

Designs for phase I trials in general and combination drug phase I trials in particular are facing several challenges with the increasing diversity of classes of agents and mechanisms of action. In addition, these new classes of anticancer agents are often administered continuously rather than intermittently, and they manifest safety profiles that are completely different from those of conventional cytotoxic agents. Determining the best dose for new combination drug treatments will have to be balanced against these aspects. Longer observation periods than the usual 3–4 weeks are required, given that continuously administered drugs may show relevant toxicity only after a prolonged exposure.[1] There are currently approximately 850 agents in the development for cancer treatment,[2] which could potentially be combined into approximately 400,000 two-drug combinations, not to mention potential combinations involving already marketed agents. Computational modelling of new drug combinations may be a way forward, but as long as this has not been developed, we will have to work with realistic phase I study modelling and planning.

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2. Rationale

A phase I study of a new combination of drugs is only the first clinical step in the development of that specific combination and should be considered a means, not an end in itself. Before commencing a combination drug phase I trial, a plan for (tumour-type specific) subsequent developmental phase II/III studies must clearly be defined. The choice for tumour type should be based on a scientific rationale, ideally including data in an appropriate preclinical model or on the basis of clinical results for the individual agents.

3. It all starts with an hypothesis

A single ideal template to perform a combination drug phase I trial will likely never exist. Every trial has to be designed based on prior knowledge of the preclinical and clinical pharmacology of the individual agents. Given the enormous number of potential combinations, in addition to a proper rationale and further development plan as outlined above, an appropriate hypothesis to guide the protocol design is also crucial. We have identified three potential general hypotheses for such studies. Whilst the hypothesis is leading for the trial design, one should obviously always keep an open eye to detect unexpected observations.

3.1. *Type 1 hypothesis: interaction at the pharmacokinetic (PK) level*

Data on metabolism and pharmacokinetics of each of the drugs involved may suggest a potential interaction at the PK level, for example, if drug A is a putative CYP3A4 inhibitor while drug B is a substrate for CYP3A4. PK drug interactions are particularly plausible when both drugs are oral, as there may be unanticipated interactions related to drug absorption and/or first-pass metabolism.

Obviously, in phase I trials based on this hypothesis extensive PK sampling is warranted, and the design will have to include PK of the single agent(s) as well as of the combination. This means that a single agent dose will have to be a part of the design, and intrapatient and interpatient variabilities will have to be taken into account (Fig. 1).

If the hypothesised interaction would lead to an anticipated increased drug exposure, the first dose-level should be defined cautiously low. Given the hypothesis, dose-escalation to the next cohort can only take place once the PK-analysis in the previous cohort is completed and can be taken into account. The outcome of this analysis can upfront be incorporated in the projected dose-levels, by introducing PK-based dose-escalation rules, such as, for instance, 'If steady state of drug A increases less than factor X due to the addition of drug B, and no dose-limiting toxicity (DLT) is observed: escalate to dose-level 3. Otherwise escalate to dose-level 2.'

3.2. *Type 2 hypothesis: interaction at PD level without interaction at PK level*

In some combinations no PK interaction is anticipated based on the respective single agent data, but evidence supports a potential PD interaction, like an increase in a specific toxicity or an additional effect on a mechanism-related biomarker. In these studies neither extensive PK-sampling nor a run-in single agent phase would be required. However, limited PK-sampling may be advisable to enable verification that the right hypothesis was chosen and to allow exclusion of a totally unexpected PK interaction as a cause in case of observed excessive toxicity. Such limited sampling can be done at each dose-level or only in dose-expansion cohorts at the maximally tolerated dose (MTD).

Obviously, the follow-up assessments of patients should be scheduled in a way that optimal monitoring of the toxicity for which an interaction is anticipated can be ensured. The follow-up schedule can be different for a combination in which QT-interval prolongation is expected during the first 5 days after intravenous administration of drugs A and B as compared to a combination in which a prolonged neutropaenia between day 10 and day 20 is anticipated after intravenous administration of drug A and daily oral administration of drug B.

3.3. *Type 3 hypothesis: no interaction at PK or at PD level*

This hypothesis would render the phase I part of a developmental path extremely short. All we need to know is the feasibility of the drugs involved given at their respective recommended single agent doses. The challenge will thus be to factor this feasibility part into the phase II trial design.

In case of a Type 1 or 2 hypothesis a phase I study has to define one or more MTDs (see paragraphs 4, 5 and 6), in contrast to a Type 3 hypothesis in which just the feasibility at one or limited dose levels has to be shown (paragraph 7).

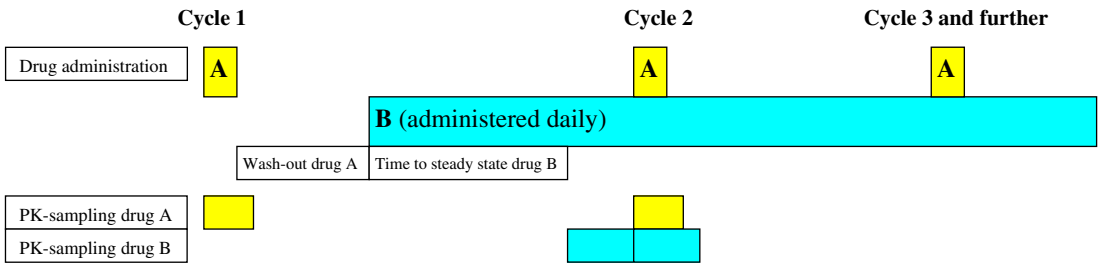

Fig. 1 – Single agent as well as drug combination pharmacokinetic analysis enabling intrapatient evaluation. Drug A is administered i.v. every 3 weeks and drug B is administered orally every day.

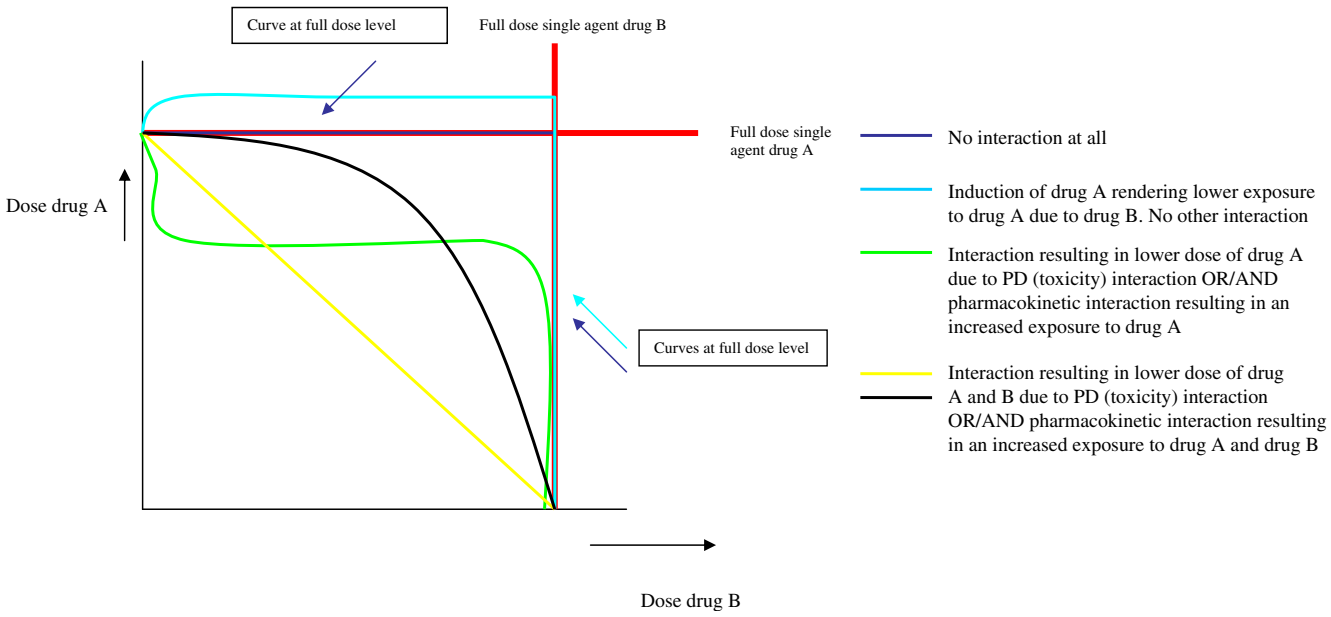

Fig. 2 – Sample of envelopes of tolerability (as types of envelopes are infinite) of a two-drug combination. An established MTD will be a single point on its curve. And although often only a single MTD is determined, many more MTDs do exist. The location of the determined MTD on its envelope is often a result of trial design.

4. Defining the MTD in Types 1 and 2 studies

In theory the number of MTDs of two drugs is infinite and does describe a curve, which we can call an envelope of tolerability. Obviously, the full envelope of tolerability of a drug combination will never be described, but defining multiple MTDs as derivatives of the envelope will generate knowledge on the dosing-range of the combination (Fig. 2).

At first glance, the MTD often seems to be determined by the data generated during the trial. However, some choices made with regard to the pre-defined dose and dose-escalation steps are crucial and will have an impact on the MTD(s) defined: the drug schedule and administration sequence, order of pre-defined escalation steps and whether or not to compromise on a dose of an active agent.

4.1. *Drug schedule and administration sequence*

Additive or synergistic effects of combinations of agents may be dependent on specific drug scheduling and will have to be taken into account. For example, combining sunitinib (standard schedule 4 weeks on, 2 weeks off) with capecitabine (standard schedule 2 weeks on, 1 week off) will have to lead to choices regarding the drug-administration schedules. In this example, if a direct drug–drug interaction is anticipated with respect to exposure to either drug due to the other (or its metabolites), then a constantly changing drug exposure might result if the common single agent on/off schedules are applied. Other potential schedules would lead to more consistent drug exposures and the choice of which schedules to explore in a phase I trial should preferably be supported by data from preclinical studies. Similar issues could arise when an intravenously administered drug is combined with an oral agent.

Furthermore, the sequence in which the drugs are administered might impact on tolerability and/or efficacy. Particularly for drugs with a short half-life a PK interaction could necessitate specific sequences of administration. But also PD interactions will have to be taken into account, when selecting the best sequence of administration.

4.2. *MTD depends on escalation steps*

As previously described, solely on the basis of a different use of the pre-defined dose-escalation steps, at least four different MTDs can be determined in a 'simple' combination phase I trial involving only two drugs (Fig. 3).[3] As mentioned earlier, the true number of MTDs is infinite, so even this represents a crude way to define the envelope of tolerability.

In considering issues such as schedule, sequence and escalation steps, one might not want to limit to the identification of only a single MTD. It might even be preferred to study different schedules and drug-sequences and thus identify a multitude of MTDs in a single phase I combination study. Given the fact that phase I trials are aiming to define tolerated doses, and cannot identify the most optimal schedule, the identified multiple MTDs can subsequently be studied in a randomised phase 2 trials to pick the winner.

4.3. *Compromising on the dose of an active agent?*

Intuitively, physicians are reluctant to lower the dose of an agent known to be active. Although this is understandable in daily oncology practise, it may in theory be incorrect and hamper the options of exploiting a possible synergistic or additive effect. So, for most combinations, one should be prepared to (initially) compromise on the dose of an active agent, however, there may be rational exceptions to this. First of all,

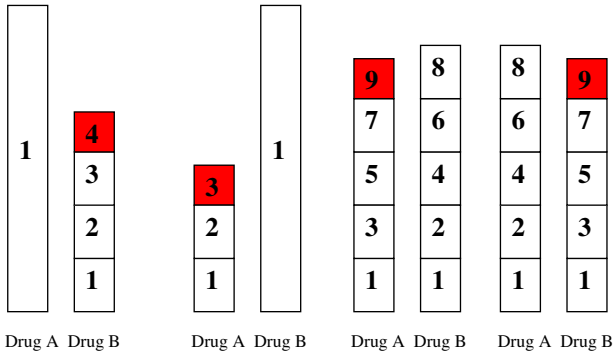

Fig. 3 – Four maximally tolerated doses (MTDs) determined with two drugs, solely depending on escalation steps. (Numbers are dose levels. Red blocks are the dose-levels exceeding the MTD.)

in a curative multimodality treatment in which a systemic agent is used as a radiosensitiser, the study population will not be a standard phase I population without further treatment options, but will consist of patient in whom cure is the goal. Lowering the dose of radiation might reduce the chances of cure, in return for an unknown benefit. On the other hand, no other population can be identified to study potential beneficial combinations during radiotherapy, so a very trial-specific approach should be defined.

Secondly, if the mechanism of action of the added agent, for example, a poly(ADP-ribose) polymerase (PARP)-inhibitor, is clearly dependent on the *in vivo* effects induced by the standard treatment, it is logical not to compromise on the dose of the standard treatment. The rationale of adding a PARP-inhibitor to conventional cytotoxic therapy, like a schedule of carboplatin and paclitaxel, is the inhibitory effect of a PARP-inhibitor on the repair of DNA-damage caused by alkylating agents. Applying the full dose of the cytotoxic therapy ascertains that the circumstances to determine the most rational MTD are optimised.

A third exception applies to studies incorporating agents, known to be almost inactive below a given standard dose, such as ifosfamide, and can fix the dose of that agent, but the involved protocols should include a clause allowing a decreased dose of that agent if pharmacokinetic studies show an increased exposure due to drug–drug interactions.

5. Interaction at PD level focusing on toxicity

5.1. *MTD/DLT-incidence in perspective of known toxicity profiles*

Combination phase I studies should preferably be initiated if knowledge is available on the single agent toxicity profile of the involved agents. Combination phase I trials should aim to model the toxicity as function of dose and PK. While defining the limits of 'tolerability' based on an incidence of unacceptable side-effects is relatively straightforward in single agent phase I trials, this turns out to be more difficult for combination phase I studies. And yet defining MTD and DLT is critical to the outcome of these studies.

A few rather philosophical questions need to be addressed for combinations in which one of the two agents already has a high incidence of dose-limiting toxicities: how to handle a limited increase in DLT-incidence that crosses the classical phase I DLT-incidence cut off (33.3%) due to the addition of the second drug? For example, docetaxel has a high incidence of febrile neutropaenia (25–35% of patients) and most of these events occur during the first cycles of treatment. In combination with docetaxel, even agents with a very limited febrile neutropaenia rate in theory can raise the incidence of this dose limiting side-effect above the classical upper boundary of acceptability. So for each trial a choice has to be made whether or not it is acceptable to shift this boundary upwards.

Another issue is whether the definition of tolerability should be approached differently if the two drugs have overlapping limiting side-effects as compared to a combination with non-overlapping toxicity. If, for instance, drugs A and B are both dose limited by diarrhoea at an incidence of 25% and 20%, respectively, it is highly likely that diarrhoea will be the DLT of the combination as well (Fig. 4). In this circumstance, there is no rationale to be more liberal in setting the limits of acceptability of toxicity, by allowing a higher incidence of this specific toxicity to define DLT/MTD. If more liberal criteria would be applied in this case, they could just as well be applied for defining DLT/MTD of the respective single agents.

More difficult are situations with non-overlapping toxicity, adding drug C (with a hypertension incidence of 20%) to the same drug A. No standard recipe can be given here and the design should anticipate on two different scenarios: non-overlapping toxicity can occur in the same patients (rendering an incidence of toxicity of 25%) or in other patients with a potential incidence of toxicity up to or even above 45% (Fig. 4).

5.2. *Type of toxicity and duration of observation*

It remains a matter of debate, also in single agent phase I studies, whether short lasting and more chronic toxicity should have the same impact in defining the DLT and therewith the MTD. In combination phase I trials, this is even more complex, especially given the fact that many phase I trials are studies combining cytotoxic therapy with agents more specific to the cancer (cell). Due to the chronic exposure during treatment with the latter, the resulting toxicity usually also has a chronic character and can affect the tolerability by other means than the more acute toxicity related to cytotoxic therapy.

Cumulative toxicity is known for some conventional cytotoxic agents such as doxorubicin (cardiotoxicity), taxanes, oxaliplatin (both neuropathies) and etoposide (leukaemogenic) and is just as important in determining the possible maximal total duration of therapy as is the dosing per cycle. Long-term toxicities are frequently only recognised just prior to or after registration of an agent. This may also be true for the more modern cancer (cell) specific agents (e.g. cardiotoxicity due to sunitinib[4]) and in early stages of drug development it will be unknown if lowering the dose per administration will allow drug administration for a more prolonged period of time. Incorporating such evaluation time frames will render

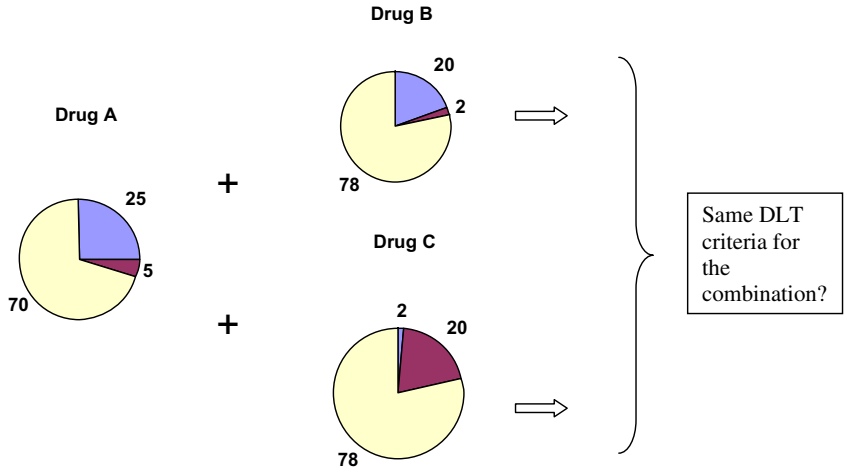

Fig. 4 – Toxicity in the same domain versus non-overlapping toxicity. DLT = dose-limiting toxicity.

phase I trials undoable. This type of toxicity can best be explored in (randomised) phase II trials.

6. Avoiding background noise on toxicity

One of the challenges in conducting combination drug phase I trials is to carefully weigh whether or not the frequency of observed toxicity is representative for the novel combination or that, due to chance, the toxicity attributable to just one of the drugs occurs in the trial in a higher than usual incidence.

Two instruments may be helpful by valuing the toxicity data generated more carefully: (1) the 3 + 3 + 3 design and (2) introducing control groups into phase I studies.

6.1. *The 3 + 3 + 3 design*

The classical 3 + 3 design allows dose-escalation based on the frequency of encountered DLTs. If in a cohort of three patients no DLTs are encountered, the next dose-level will be explored. In the case of two DLTs out of three patients, the MTD is considered exceeded, and a lower dose level is further evaluated for its MTD potential. In the case of one DLT out of three patients, an extra three patients are enroled at that dose-level. If two or more DLTs occur in six patients, the MTD is considered exceeded.

By using the classical 3 + 3 design, implicitly an incidence of <33.3% of severe toxicity is considered acceptable, whereas determining this incidence is based on a very limited number of patients.

The chance that dose-escalation is 'falsely' halted is intrinsically related to the incidence of the severe toxicity of the new drug combination. This incidence is off course unknown, but prior data may point towards a relatively high incidence of severe toxicity, making the investigators eager to address this issue before commencing the trial.

By using the classical 3 + 3 design in a drug combination phase I trial with an unknown but true incidence of severe toxicity of 5% the chance of a 'falsely' halted dose-escalation can be calculated by using formula 1 and is: 3%, but it rapidly increases to 29% and 51% if the unknown but true incidence of severe toxicity increases to 20% and 30%, respectively (Table 1).

Formula 1a : $x^3 + 3 * (x^2 * y + x^2 * y^2 + x^2 * y^3 + x^2 * y^4)$

Table 1 – Chances of falsely halting dose-escalation as a function of the Incidence of unknown but true severe toxicity and the trial design.

		Chance of 'falsely' halting dose-escalation using classic 3 + 3 design; (formula 1)	Chance of 'falsely' halting dose-escalation using 3 + 3 + 3 design (incl 2 of 3*); (formula 2)	Chance of 'falsely' halting dose-escalation using 3 + 3 + 3 design (excl 2 of 3*); (formula 3)
Incidence of unknown but true severe toxicity	Formula parameters			
5%	x = 0.05 y = 0.95	0.03	0.01	0.01
20%	x = 0.20 y = 0.80	0.29	0.19	0.22
30%	x = 0.30 y = 0.70	0.51	0.42	0.44

* 2 of 3 refers to two dose-limiting toxicities (DLTs) occurring in the first three patients in a specific dose-level.

OR

$$\text{Formula1b}: 1 - \{y^3 + 3 * y^5 * x\}$$

(x = unknown but true incidence of severe toxicity; $y = 1 - x$).

The recently briefly mentioned 3 + 3 + 3 design[3] decreases the chance of 'falsely' halting dose-escalation by means of the addition of enrolment of three extra patients at the same cohort as soon as two DLTs in six patients are observed. The extra three patients do allow the investigators a more refined grip on the incidence of severe toxicity of the treatment under evaluation. This strategy will result in a decrease of 'falsely' halting dose-escalation from 29% to 19% (by itself a reduction of approximately one-third!) if the unknown but true incidence of severe toxicity is 20% as can be calculated from formula 2 (Table 1).

$$\text{Formula 2}: 1 - \{y^3 + 3 * y^5 * x + 12 * y^7 * x^2\}$$

A specific issue that needs some extra thought is the situation of two DLTs occurring in nine patients. From a mathematical viewpoint, it does not matter if these two DLTs occur in the first three patients or in the last three patients. The latter situation will never occur, given the fact that after 0 DLTs in the first three patients, the dose will already be escalated after these three patients. It is more delicate how to handle the situation of two DLTs in the first three patients. In the classic 3 + 3 design, this would be the signal for exceeding the MTD, as a further expansion of three patients will not get the incidence below 33.3%. But in the 3 + 3 + 3 design, there is a chance that the following six patients are without a DLT rendering an incidence of severe toxicity below the threshold of 33.3%. In our opinion this is not worthwhile, based on the following two arguments.

First of all, if in two of three patients a DLT has occurred, while the true but unknown incidence of severe toxicity is 30%, the chance of ending up with just two of nine is 12%. So even if the incidence is within the acceptable range, only 1 of 8 trials will succeed to prove so.

The second argument against dose-expansion in the presence of two DLTs in the first three patients is that it facilitates 'falsely' continuing dose-escalation to a greater extent than it limits 'falsely' halting dose-escalation. The chance of 2 of 3 will occur in 14 of 100 trials in which the true but unknown incidence is 25%, whereas this occurs in 29 of 100 trials if the unknown incidence of severe toxicity is 40%.

So, applying the 3 + 3 + 3 design excluding the '2-out-of-the-first-3-situation' is the same as applying the 3 + 3 design and only in the case in which after expansion to six patients two DLTs are observed, a further expansion to nine patients will be done. The advantage of this approach can be calculated with formula 3, and examples are shown in the last column of Table 1.

$$\text{Formula 3}: 1 - \{y^3 + 3 * y^5 * x + 9 * y^7 * x^2\}$$

It is clear that the 3 + 3 + 3 design is only of additional value if the incidence of severe toxicity is anticipated to be in the upper range of what may be considered acceptable. On the other hand, there is no harm done by applying this to all phase I trials, as it will only be used at a point where the classic phase 3 + 3 design already definitely has halted dose-escalation.

6.2. *Introducing controls in phase I studies*

Diminishing the effect of chance by introducing a control population is a standard procedure in phase II and III trials, rendering results better interpretable for a larger population. In phase I studies in the field of oncology controls have not been used up to now. However, particularly in combination phase I studies they might help in distinguishing added toxicity related to the added drug, from the toxicity related to the backbone standard.

6.2.1. *Each patient its own control*

Using every patient as his or her own control is a simple way to introduce a controlled situation. In cycle 1, for instance, the patients can be treated with drug A, followed by a second cycle in which the combination of drug A + B is administered, without changing the dose of drug A (Fig. 5). This approach will generate information on additional toxicity due to the added agent and leans on the premise, as discussed in Section 4, that thoughts are given to the increment in toxicity that is allowed. In this model, dose-escalation decisions should relate to the increment in toxicity between cycles 1 and 2 but also include rules with regard to the absolute incidence of toxicity. If this latter is not incorporated, the following might occur: 3 of 3 patients experience febrile neutropaenia during cycle 1 (not imaginary as this will happen in 2% of cohorts of three patients treated with docetaxel). No matter how many episodes of febrile neutropaenia do occur in cycle 2, there will be no increment in toxicity and dose-escalation will be done.

This model has some major limitations that need to be addressed in each specific trial to which it is applied. For example, most usually a preventive measure (like dose-reduction) is taken to avoid repetition of toxicity observed in the previous cycle, whereas in this model the single difference between cycles 1 and 2 should only be the addition of drug B and not a change in dose. Replacing these patients, on the basis of non-evaluability, is not appropriate as it results in an observation bias rendering an underestimation of toxicity.

If this model is applied, then only agents can be used of which the toxicity has completely disappeared at the start of cycle 2 and that do not have cumulative toxicity. For example, combining oxaliplatin with placebo might result in an increment in neurotoxicity that falsely would be assigned to the placebo.

6.2.2. *Each patient its own control plus randomisation*

A second control-method can be added to the model described in the previous paragraph by using a randomisation between a group of patients treated according to the model described in paragraph 5.2.1 and a group of patients treated with the combination from the start. This generates intrapatient information as well as information between the two cohorts of patients. Obviously defining the dose-escalation rules for this double-controlled phase I trial will be equally challenging (Fig. 6).

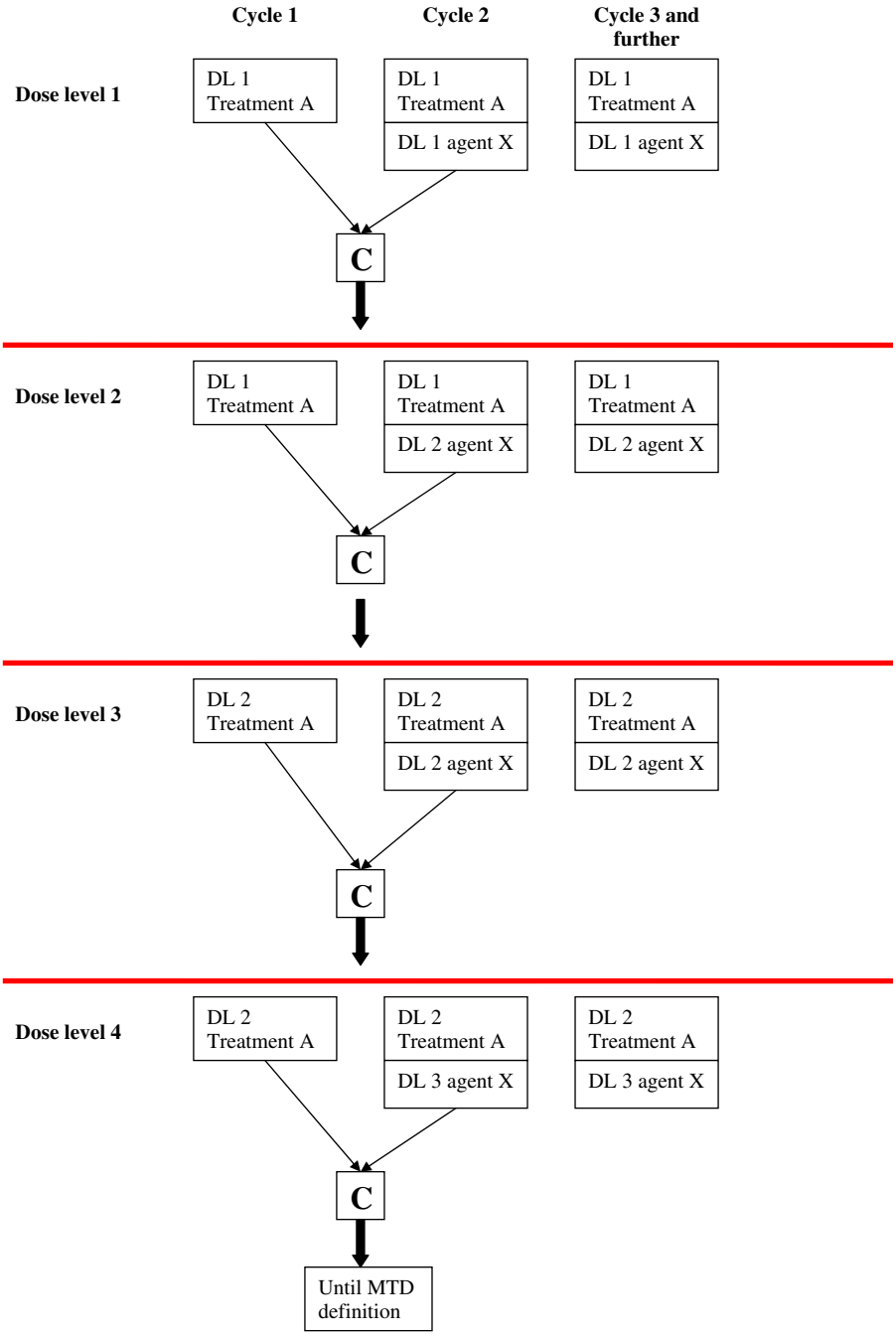

Fig. 5 – Using each patient as its own control to decide on dose-escalation. Treatment A can be either standard treatment or an investigational drug. C : compare and if within pre-defined criteria: escalate. DL: dose-level; MTD: maximally tolerated dose.

6.2.3. Bayesian approach

This strategy is proposed to deal with the issue of background toxicity if an agent is added to standard treatment, especially for treatments with curative intent, for example, chemo-radiotherapy for locally advanced head and neck cancer, given the fact that alterations in the standard treatment can compromise survival. Due to coinciding differences in patient group characteristics, the observed incidence of severe toxicity might be higher than that expected, even if the added agent was dosed at placebo-level. To circumvent the issue of background noise, the Bayesian approach introduces, next to enroling controls at each dose-level, adaptive (continual reassessment) design.

However, if a new agent is added to the standard treatment, the incidence of observed toxicity in the trials designating the standard treatment as standard can be used as the *a priori probability* of severe toxicity by means of an adaptive design, by invoking a Bayesian approach. Differences in the settings of the current and the pivotal trial can be accounted for in the prior probability. The prior probability should be clearly defined before enroling the first patient.

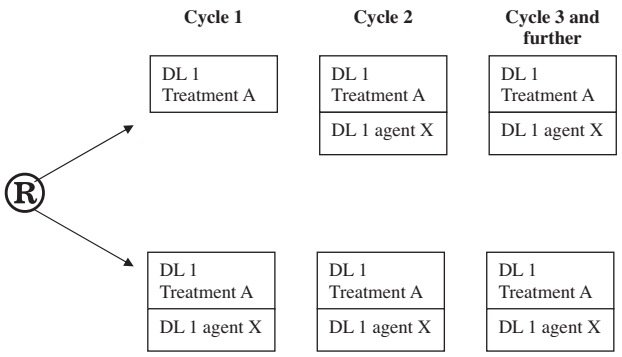

Fig. 6 – At each dose level there is an intrapatient comparison (like that in Fig. 4) and an interpatient comparison (between the two arms) before deciding on dose-escalation.

As a small number of controls are enroled at each dose-level (Fig. 7), safety data generated in the control group, across the dose-levels, are combined with the *prior*, resulting in a more stable and importantly a more robust estimate of the background toxicity in that specific population treated solely with the standard treatment. So, the impact of the initial *prior* will thus decrease as more control data are gathered.

Then, at each dose-level that estimate is used to relate the observed toxicity in the group treated with the additional agent added to the standard treatment, to correct for coincidence as well as patient selection issues. It is important to note that the adaptive design of the Bayesian model uses accumulated data of patients treated solely with the standard treatment at all previous dose-levels to decide on dose-escalation (Fig. 7).

A Bayesian approach renders probabilities, and that is an important difference that definitely needs a change in mind-set of phase I investigators. Such a probability is presenting the data in the opposite way as we are used to in phase I trials, as usually we interpret incidence data in small groups of patients, deliberately ignoring the large uncertainties inherently related to a limited sample size.

7. Determining feasibility in Type 3 studies

If no PK or PD interaction is anticipated, the feasibility of a combination can be proven in a kind of phase I/II trial. If we assume that drug A is already regarded as standard treatment for a certain tumour type, then patients with this tumour type can be enroled in a trial in which all patients start with a combination of drug A and drug B, both at full dose. Such an approach is feasible in, for example, the non-small lung

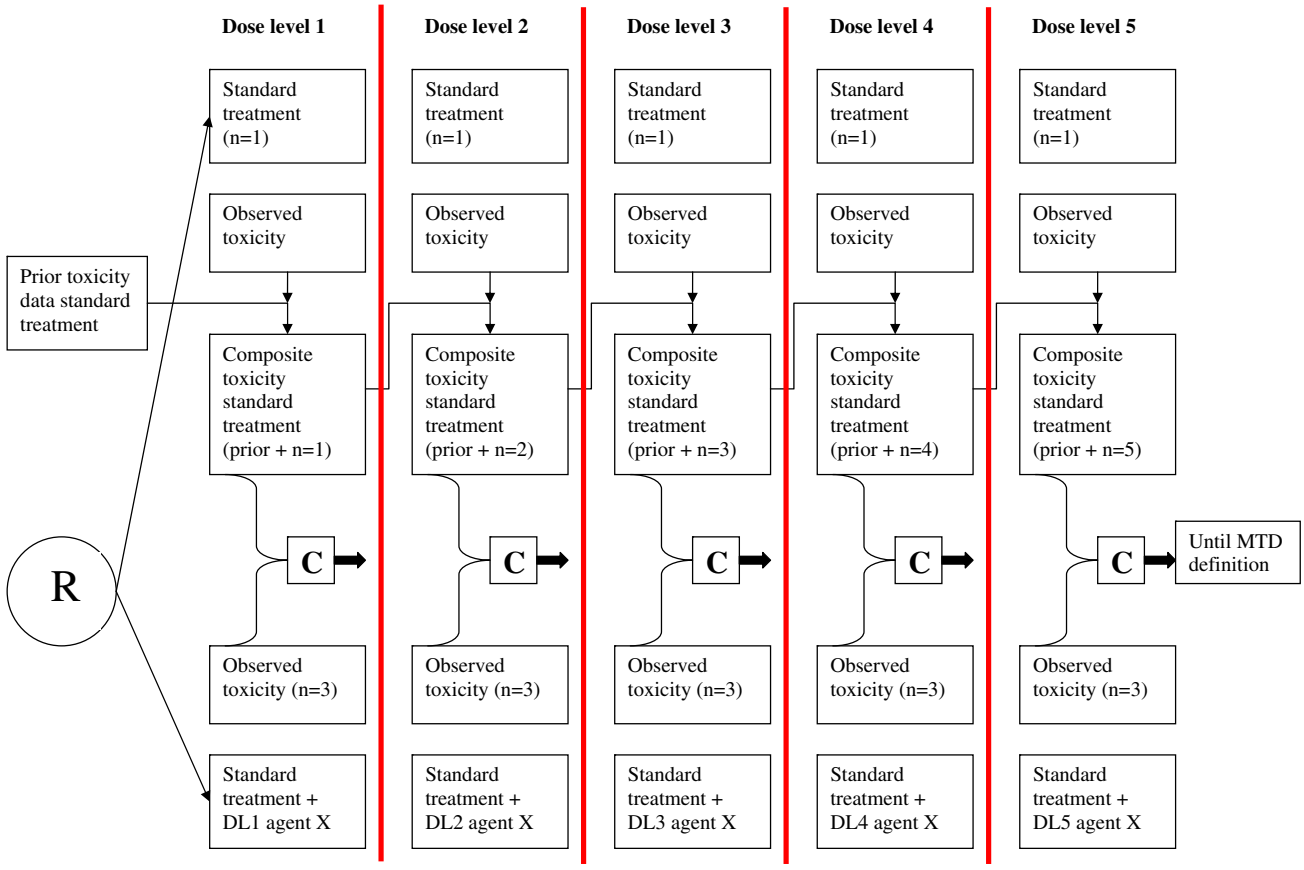

Fig. 7 – Randomised phase I drug combination trial in which an agent is added to standard treatment: continual reassessment of toxicity of the standard treatment in order to compare the toxicity of the new combination to controls. C: compare and if within pre-defined criteria: escalate. DL: dose-level; MTD: maximally tolerated dose. *n* = 1 and 3 are arbitrarily chosen to support the illustration.

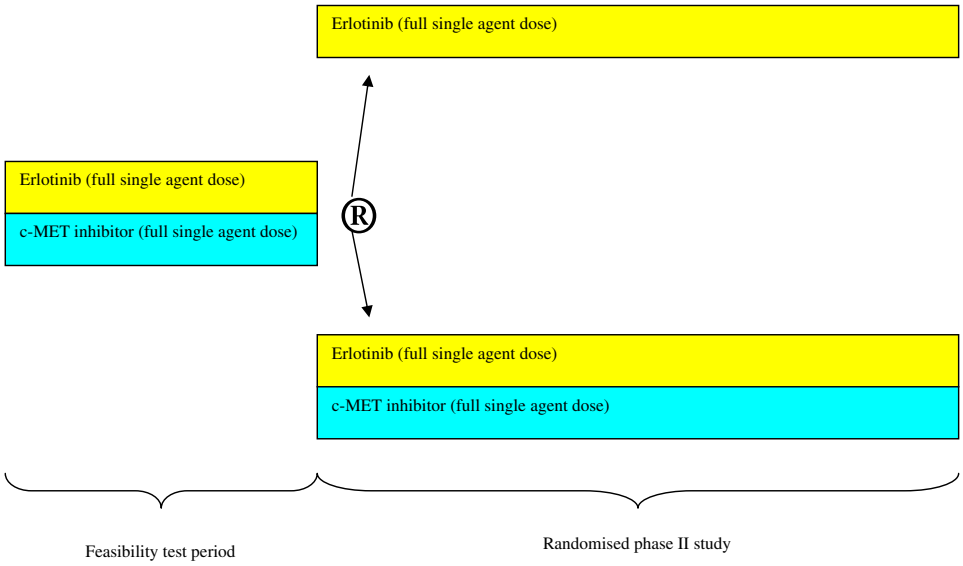

Fig. 8 – Testing of feasibility in drug combinations in which no pharmacokinetic or pharmacodynamic interaction is anticipated and one of the agents is regarded as standard treatment for this population. As example: erlotinib, regarded as standard therapy, is combined with a novel c-MET inhibitor. ®: randomisation.

cancer patient population in which the epidermal growth factor inhibitor erlotinib is combined with a novel c-MET inhibitor of which single agent MTD already has been determined. After the first treatment period (the feasibility-test period) randomisation can be performed between drug erlotinib plus or minus the c-MET inhibitor rendering a randomised phase II population (Fig. 8). In stead of the classical DLT rules applied in phase I trials, this type of trials should incorporate go/no go rules based on a safety-interim evaluation observed in the first treatment period in a pre-defined number of patients.

A more conservative approach would utilise two cohorts, beginning with full dose of drug A combined with slightly lower dose of drug B. If the safety-interim analysis does not detect an excess of toxicity, then subsequent patients can be enroled in the cohort using full dose of both drugs.

8. Conclusion

Dose-finding studies are the first step in the clinical development of new combination treatment strategies. Combination phase I studies are extremely complex. Designing phase I studies is as important as the conduct itself and should be done by dedicated phase I researchers since a standard template cannot be made.

If there is a rationale to develop a specific drug combination, a hypothesis should be generated. This hypothesis, based on the anticipated levels of interaction, will be guiding for the design of the phase I study, although one should always be open to detect the unexpected. A strong consideration is to design studies aiming to potentially determine multiple MTDs with final dose determination in randomised phase II trials. Introducing controls and the 3 + 3 + 3 design are strategies allowing more grip on combinations with high incidence of severe toxicity. Key opinion leaders in the field of phase I oncology trials should make joint considerations towards future trial design in combination phase I studies.

Conflict of interest statement

None declared.

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