The Development of Phase I Cancer Trial Methodologies: the Use of Pharmacokinetic and Pharmacodynamic End Points Sets the Scene for Phase 0 Cancer Clinical Trials

A. Hilary Calvert and Ruth Plummer

Abstract

Although the concept of a phase 0 trial is a relatively new one, there has been a slowly increasing trend toward basing early clinical trial designs on pharmacokinetic and pharmacodynamic end points that has been developing over many years. This article will review the early cancer trial methodologies and the various techniques that have been used to refine them. Several illustrative examples will be presented showing their relevance to trial designs using pharmacodynamic end points and targeted agents. Some criteria for characterizing suitable phase 0 end points are suggested. Four trial designs that are essentially developed for cytotoxic agents using the maximal tolerated dose as an end point are described. Although these trials were not designed with the use of more sophisticated pharmacodynamic end points (such as the measurement of the effect of a targeted agent on its target), they have been developed to optimize the speed with which a dose needed to achieve a particular effect can be determined and are, to this extent, relevant to the design of studies with pharmacodynamic end points.

The Traditional Phase I Trial

The phase I trial designs for anticancer agents have, in the past, differed from those of other therapeutic agents. Because most anticancer agents were antiproliferative agents, they had potentially life-threatening side effects to proliferating normal tissues such as the bone marrow and the gastrointestinal epithelium. Further, because the biochemical or biological differences between normal and tumor tissues are small, these drugs have a low therapeutic index, so that it is necessary to use a maximally tolerated dose (from the point of view of toxicity) to elicit any anticancer effect. For example, phase I trial of an antihypertensive agent would be done on normal volunteers and have a pharmacodynamic end point, the reduction in blood pressure. Although a phase I trial of an anticancer agent involves escalating doses to a defined end point, there are a number of differences. It would typically be done in cancer patients with a limited prognosis because of the concern of the potential genotoxicity of most of the anticancer agents. The end point of the trial would be toxicity to ensure that the maximally tolerated dose was used in phase II, which, in turn, would maximize the probability of seeing an anticancer effect. A further complication is that there is considerable interpatient variability in the tolerance of anticancer drugs.

The traditional design for a phase I study of an anticancer agent arose from this background. A starting dose is selected, designed to be safe based on animal toxicology studies. Patients are treated in cohorts, normally of three, to allow some idea of interpatient variability to be obtained. Doses are escalated to a maximum tolerated dose (MTD), defined by toxicity. The size of the increments between successive dose levels is progressively decreased as toxicity is seen, frequently using a progression known as a modified Fibonacci series (although it bears little resemblance to an unmodified Fibonacci series). These trial designs have been developed by many individuals and organizations over many years and have been described by Storer (1). Typical dose escalation schemes are shown in Table 1.

Although this design will reliably identify the MTD of a drug, there are, however, a number of shortcomings. It may require a large number of patients and a long time to complete, especially if the estimate of the starting dose was low compared with the final MTD. This design is not only costly but also results in a high proportion of the patients being treated at doses so low that a therapeutic effect is unlikely. Although the documentation of antitumor activity is not a primary objective of a phase I trial, it is desirable to maximize the chance of it occurring. Patients inevitably have advanced and incurable cancer and hope for a therapeutic effect although the information they have been given and the consent they sign say that this is unlikely. Further, early indications of therapeutic activity are being increasingly used to decide which agents to progress to phase II and phase III development. These considerations led to the investigation of more efficient designs for trials with three main objectives: (a) to treat fewer patients altogether, to make them more efficient; (b) to treat a greater...
Pharmacokinetic guidance is a strategy that uses pharmacokinetic data to guide dose escalation in phase I trials. This approach has been developed to improve the design of phase I trials and to enhance the safety and efficacy of new anticancer agents. The potential for using pharmacokinetic studies to improve the design of phase I trials was proposed by Collins et al. (2) in 1986. A number of anticancer agents that had undergone phase I trials were studied in animals and in man, and the comparative pharmacokinetics between species evaluated. It was noted that whereas the MTD (expressed in mg/m²) differed widely (10-fold) between mice and humans, when the systemic exposure was measured as the area under the concentration-time curve (AUC) of the plasma level of the drug concerned, the variability between species was much reduced. On average, the ratio of the AUCs at the MTD was close to 1, with most drugs being between 0.6 and 1.3. A few drugs (notably antimetabolites) lay outside this range. These observations led to the proposal that a phase I trial could be conducted with a rapid escalation to a dose that was close to the MTD in the following manner: the AUC at the MTD could be determined experimentally in an appropriate animal species, and this value determined as the target AUC for the trial. When the first cohort of patients was treated, clinical pharmacokinetic studies could be used to estimate the AUC at the starting dose. The ratio of this AUC to the target AUC could then be used to guide the next dose escalation to bring the dose close to the anticipated human MTD, with suitable margins for error and safety incorporated in the scheme. This pivotal (2) article led to an increasing awareness of pharmacokinetics and pharmacodynamics and their role in the conduct of early trials of anticancer drugs in humans. In 1987, the European Organization for Research and Treatment of Cancer Pharmacokinetics and Molecular Mechanisms Group published a study (3) of the factors affecting a pharmacokinetically guided dose escalation. These included assay availability, plasma protein binding, nonlinear pharmacokinetics, interpatient variability, species differences, and chronopharmacology. Pharmacokinetic guidance has been used successfully in many trials, but two examples will illustrate some potential issues that have to be considered.

Gianni and colleagues (4) conducted a phase I trial of iododeoxyuridine (IDOX) using pharmacokinetics to guide the escalation. It was known that an active metabolite (IDOXOL) was produced that had a similar toxicity to IDOX against human granulocyte colony stimulating factors. In mice, the IDOXOL levels were only ~20% of the IDOX levels, but in humans the conversion was more rapid and only ~10% of the total AUC was accounted for by IDOX. These pharmacokinetic and pharmacodynamic observations permitted a more rapid dose escalation to be accomplished, taking into account the conversion to IDOXOL. By these means, the number of cohorts required to complete the trial was reduced.

Foster et al. (5) attempted to conduct a pharmacokinetically guided phase I trial of losoxantrone, an anthrapyrazole-based drug with some structural similarities to mitoxantrone. At the starting dose of 5 mg/m², there was a 4-fold variation in the plasma AUC among the three patients in the cohort. Interpatient variability continued to be very wide at higher doses, at no point permitting the dose necessary to achieve the target AUC to be estimated with any confidence. The dose escalation was completed in a traditional manner, and the AUC at the MTD was ~3-fold higher than the target AUC determined in mice (6). These results are illustrated diagrammatically in Fig. 1.

One explanation for these results is that, in this case, the plasma AUC does not reflect the exposure of the critical target tissue to the drug. Losoxantrone showed a very rapid distribution into the tissues (6), and the myelotoxicity was related more closely to the total dose given than to the plasma AUC.

The concept of pharmacokinetic guidance, although it may often be difficult to implement, has contributed greatly to the development of early trial methodologies in cancer by focusing attention on the importance of functional end points in trials.

### Table 1. Mathematical series potentially used for the dose escalation in phase I trials

<table>
<thead>
<tr>
<th>Dose</th>
<th>Incremental ratio</th>
<th>Dose</th>
<th>Incremental ratio</th>
<th>Dose</th>
<th>Incremental ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>—</td>
<td>1</td>
<td>—</td>
<td>1</td>
<td>1.41</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1.41</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>2</td>
<td>2.83</td>
</tr>
<tr>
<td>5</td>
<td>1.66</td>
<td>1.66</td>
<td>1.66</td>
<td>2</td>
<td>2.83</td>
</tr>
<tr>
<td>8</td>
<td>1.60</td>
<td>1.60</td>
<td>1.60</td>
<td>2</td>
<td>2.83</td>
</tr>
<tr>
<td>13</td>
<td>1.625</td>
<td>1.625</td>
<td>1.625</td>
<td>4</td>
<td>5.66</td>
</tr>
<tr>
<td>21</td>
<td>1.615</td>
<td>1.615</td>
<td>1.615</td>
<td>8</td>
<td>6.48</td>
</tr>
<tr>
<td>34</td>
<td>1.619</td>
<td>1.619</td>
<td>1.619</td>
<td>8</td>
<td>11.31</td>
</tr>
</tbody>
</table>

NOTE: The Fibonacci series of classic mathematics is shown on the left. This is never used in its entirety, but the most commonly used series has been the modified Fibonacci in the central two columns. This has the first three terms of the Fibonacci series but uses a geometric progression with a ratio of 1.33 after the third term. Pure geometric series, such as the one shown on the right where the incremental ratio is the square root of two, leading to a dose doubling for every two doses, are also frequently used. It is common to reduce the incremental ratio when toxicity is seen. This is probably the most logical approach and is similar to that recommended in the accelerated titration design (12). The starting dose would be defined by animal toxicology studies, but for the purpose of this table is normalized to 1, so subsequent doses represent the number of multiples of the starting dose.
and increasing awareness of their utility. The widely used dosing formulae for carboplatin (7, 8) have found a place in oncology practice all over the world and are derived from these concepts.

Continual reassessment methods. Proposed by O’Quigley in 1990 (9), the continual reassessment method (CRM) does not rely on any pharmacokinetic or pharmacodynamic physiologic models, but models the statistical probability of an MTD occurring at a particular dose based initially on prior assumptions. As the dose escalation progresses, the data obtained are used to modify the model and obtain new estimates of the relationship between dose and MTD. This method has several potential advantages: no hypotheses with regard to the mechanism of the drug in question are needed; it has the potential to permit a very rapid escalation to a dose close to the final MTD minimizing the number of patients treated at nontherapeutic levels; it also uses the data obtained from all dose levels for the final model and permits a level of statistical confidence to be attributed to the MTD. A potential disadvantage is that the model may overshoot in the early stages, predicting a dose that is too high, and that the dose may oscillate around the MTD before the model converges. In view of this, various modified continual reassessment methods (mCRM) have been proposed (10, 11) to introduce stopping rules and reduce the chance of treating at a dose higher than the MTD, and in some cases, this has resulted in trials that may have taken longer than if a traditional method had been used (12). Although the use of CRM methods has been controversial (13), they have repeatedly been used and have clearly served to accelerate the conduct of some early clinical studies (14).

In one example, three phase I trials were done with pemetrexed (15–17). Two of these (a weekly schedule and a once every 3 weeks schedule) were done using a mCRM method (11). The third was done using a traditional method. A summary of these results is shown in Table 2. Clearly, the mCRM methods both completed more quickly and had more patients treated at doses close to the final MTD than the traditional method (18). As an investigator on the traditional design study, the author is aware that the slow completion was due to protocol requirements rather than slow accrual.

Accelerated titration design. This design was proposed by Simon et al. in 1997 (19) based on a stochastic model derived from data acquired from 20 phase I trials of nine different drugs. Four simple, practical designs were proposed, involving dose doublings while only minimal toxicity was seen, intrapatient dose escalation, and single patient cohorts. It was shown that these would have been safe and rapid in the 20 phase I trials used for the study. Although there is the possibility that the use of single patient cohorts could be hazardous if there was a large amount of intrapatient variability in tolerance, this does not seem to have been the case in practice. In the author’s experience, this design permitted the completion of a phase I study of a novel platinum analogue using only 10 patients (20). The article describing the design (19) has been cited 149 times since its publication in 1997, and it is likely that many other phase I trials have been based on the same concepts. These designs have been very widely adopted on account of their relative simplicity and practicality.

Relevance to Phase 0 Studies

In practice, most early clinical trials use elements of all the methodologies described previously. None of the methodologies previously described (traditional, pharmacokinetically guided, continual reassessment or accelerated titration), however, address our major requirement for modern targeted agents: the use of a pharmacodynamic end point that reflects the effect of the drug on its intended target. With the advent of a
large number of targeted agents, pharmacodynamic end points assessing the effect of the drug on its target are becoming more important, leading to the introduction of the phase 0 study. The rationale, conduct, and structure of phase 0 studies are described in detail elsewhere in this CCR Focus. Essentially, they permit the definition of a pharmacodynamically effective dose during a time-limited exposure to the drug, with reduced requirements for preclinical toxicology and expedited entry into the clinic (21–25). All studies, however, have in common that a dose must be determined with a degree of statistical confidence that will have a defined effect, whether that effect is measured as a biochemical phenomenon, such as target inhibition, or as a toxic end point. Thus, the basic methodologic insights that have been developed remain highly relevant to the design of phase 0 trial and those with pharmacodynamic end points.

A pharmacodynamic trial of AG014699: an example of a phase 0 segment within a phase I trial. Inhibitors of poly(ADP-ribose) polymerase (PARP) are of great interest as single agents for the treatment of BRCA-related cancers, as chemopotentiators and radiopotentiators, and in noncancer applications (26). A number of these are undergoing clinical development, including ABT-888, the subject of other articles in this CCR Focus (27, 28). The first clinical study of a PARP inhibitor in cancer patients was that of AG014699 (29). The objective of this study was to develop the combination of temozolomide with a PARP inhibitor as preclinical data indicated significant potentiation of temozolomide (30). Because toxicity was expected from the temozolomide, toxicity could not be used as an end point for the dose escalation of AG014699, therefore a pharmacodynamic end point was chosen. An assay to measure PARP activity in peripheral tissues was developed and fully validated (31). It is estimated that this took ~2 person years. The trial was then conducted in two stages. In the first stage, AG014699 was given in combination with half the normal dose of temozolomide, to add a margin of safety, in the event that the myelotoxicity of temozolomide was enhanced by AG014699. PARP activity was also measured in peripheral blood mononuclear cells. In addition, a single dose of the PARP inhibitor was given as a single agent 1 week before starting the combination treatment. This permitted the pharmacodynamic effect and any toxicity of the PARP inhibitor to be documented in the absence of any interfering agent, so that this trial could be described as a phase 0 trial encapsulated within a phase I trial. A PARP inhibitory dose was defined on the basis of preclinical xenograft experiments. This was a dose defined to achieve maximal PARP inhibition in tumor tissue (defined as a plateau in the level of inhibition between successive dose levels) in the absence of toxicity, or a dose producing a level of inhibition shown to potentiate temozolomide in a xenograft model, if toxicity occurred (29).1 When the PARP inhibitory dose was determined in peripheral blood mononuclear cells, the trial progressed to the second stage. In this stage only, patients with melanoma who consented to paired tumor biopsies were enrolled. The dose of temozolomide was then escalated to either the standard dose for temozolomide or the MTD, with concomitant measurements of PARP inhibition in tumor biopsies. It was possible to establish a PARP inhibitory dose of 12 mg/m² that caused >90% inhibition of PARP in peripheral blood mononuclear cells in part 1, and to show that a normal single-agent dose of temozolomide could be given in combination with this in part 2. Raising the dose of AG014699 to 18 mg/m², however, resulted in dose-limiting myelosuppression due to enhancement of the toxicity of temozolomide. The inhibition of PARP in melanoma biopsies at 12 mg/m² also met the protocol requirement (mean, 92%; range, 88–97%).

Subsequently, the doses defined in this study were used to conduct a study in metastatic malignant melanoma where a confirmed partial response rate of 18% and a stable disease rate (≥6 months) of 18% were observed (32).

**Interpretation of clinical trial data based on pharmacodynamic end points.** The strategy adopted for the trials of AG014699 led to the successful completion of the dose-ranging trial and to the conduct of a phase II trial that showed activity. Many questions, however, still remain. Is 90% inhibition of PARP optimal for potentiation of temozolomide activity? What is the duration of the inhibition, and would a longer duration result in a higher level of activity? Does the dose selected inhibit any of the PARP homologues (33), and if so, what effect might this have on toxicity and activity?

Considerations such as these clearly apply to any trial of an agent where the molecular target is known and where an assay exists for measuring its effect on the target in patients. There are probably only a few cases where the biological dynamics of the interaction of the drug and its target, both in the tumor and in the normal tissues, is sufficiently well understood to be sure that the correct treatment strategy has been chosen. A recent article (34) has proposed that pharmacodynamic end points should be measured as proof-of-principle that the proposed target is being affected in humans, but that the final choice of dose should usually involve escalating to some level of toxicity to ensure the maximum effect on the tumor target. Clearly, this technique will be useful in cases where the pharmacodynamic assay is not certain to reflect the effect of the drug on the target, where the required effect on the target is uncertain, or where the drug may have multiple targets. In the event that the drug fulfills the criteria suggested for phase 0 trials (22), a pharmacodynamic end point should in itself be sufficient.

---

1 Submitted for publication.
variability is a major issue, and doses must be defined with some confidence that they will achieve the desired effect in a large proportion of the patients treated. Most early trials are designed with boolean end points (an end point that can logically be either true or false, rather than one having a continuously variable value). Examples of boolean end points are the MTD, which is either achieved or not, and the PARP inhibitory dose defined in the trial of AG014699 (ref. 29; defined as a fixed event). This is illustrated in Fig. 2. In practice, most end points are continuous variables, and analytic systems designed to model the dose-response effect of a continuous variable should give us greater sensitivity, more precise confidence intervals, and a better insight to guide dosage than boolean cutoff points or ranked variables. This is illustrated hypothetically in Fig. 2. As far as the author is aware, no such systems currently exist, at least for widespread routine use. Finally, it is essential to understand the biology of the system in use. The utility of pharmacodynamically directed trial designs is dependent on the depth of our understanding of the system involved. The in vitro and animal model systems must be carefully chosen to reflect the requirements of the trial and fully validated. The magnitude and duration of the pharmacodynamic measurement associated with therapeutic and toxic effects must be understood, as must any possible off-target effects. Any differences in the results obtained on a surrogate tissue (such as peripheral blood mononuclear cells) and those on the relevant tumor must be accounted for. Phase 0 trials and pharmacologic end points will have a pivotal role to play in future cancer drug development, provided they are sufficiently thoroughly researched and executed.

**Conclusion**

Pharmacodynamic and pharmacokinetic modeling is clearly important for all trials, but is central to the concept of the phase 0 trial. Many of the techniques developed for more traditional studies where the end point is toxicity are also applicable to trials with pharmacodynamic end points. Both involve escalating doses to achieve a desired effect. In one case, this is a level of toxicity, and in the other, it is the pharmacodynamic end point. For both, it is desirable to reach the effective dose as expeditiously as possible, and patient safety is of paramount importance. For both, interpatient variability is a major issue, and doses must be defined with some confidence that they will achieve the desired effect in a large proportion of the patients treated. Most early trials are designed with boolean end points (an end point that can logically be either true or false, rather than one having a continuously variable value). Examples of boolean end points are the MTD, which is either achieved or not, and the PARP inhibitory dose defined in the trial of AG014699 (ref. 29; defined as a fixed event). This is illustrated in Fig. 2. In practice, most end points are continuous variables, and analytic systems designed to model the dose-response effect of a continuous variable should give us greater sensitivity, more precise confidence intervals, and a better insight to guide dosage than boolean cutoff points or ranked variables. This is illustrated hypothetically in Fig. 2. As far as the author is aware, no such systems currently exist, at least for widespread routine use. Finally, it is essential to understand the biology of the system in use. The utility of pharmacodynamically directed trial designs is dependent on the depth of our understanding of the system involved. The in vitro and animal model systems must be carefully chosen to reflect the requirements of the trial and fully validated. The magnitude and duration of the pharmacodynamic measurement associated with therapeutic and toxic effects must be understood, as must any possible off-target effects. Any differences in the results obtained on a surrogate tissue (such as peripheral blood mononuclear cells) and those on the relevant tumor must be accounted for. Phase 0 trials and pharmacologic end points will have a pivotal role to play in future cancer drug development, provided they are sufficiently thoroughly researched and executed.

**Disclosure of Potential Conflicts of Interest**

A. Calvert has a commercial research grant with, an ownership interest in, and has received minor honoraria from Pfizer and was the recipient of the Pfizer Award for Science Innovation, 2005.

**Acknowledgments**

We thank Alan Boddy, Fiona Chapman, Nicola Curtin, Chris Jones, and Rebecca Perret (all from the Northern Institute for Cancer Research, University of Newcastle upon Tyne, United Kingdom) for their work on the trials of AG014699.

---

**References**

Clinical Cancer Research

The Development of Phase I Cancer Trial Methodologies: the Use of Pharmacokinetic and Pharmacodynamic End Points Sets the Scene for Phase 0 Cancer Clinical Trials

A. Hilary Calvert and Ruth Plummer


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/14/12/3664

Cited articles
This article cites 33 articles, 17 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/14/12/3664.full.html#ref-list-1

Citing articles
This article has been cited by 7 HighWire-hosted articles. Access the articles at:
/content/14/12/3664.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.