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Position Paper

Endpoints and other considerations in phase I studies of targeted anticancer therapy: Recommendations from the task force on Methodology for the Development of Innovative Cancer Therapies (MDICT)

Christopher M. Booth[a,e], A. Hilary Calvert[b], Giuseppe Giaccone[c], Marinus W. Lobbezoo[d], Lesley K. Seymour[a], Elizabeth A. Eisenhauer[a,], On behalf of the Task Force on Methodology for the Development of Innovative Cancer Therapies*

[a]*National Cancer Institute of Canada Clinical Trials Group, 10 Stuart Street, Kingston, ON, Canada K7L 3N6*
[b]*Northern Institute for Cancer Research, Medical School, Newcastle upon Tyne, UK*
[c]*Medical Oncology Branch, National Cancer Institute, Bethesda, USA*
[d]*NDDO Research Foundation, Amsterdam, The Netherlands*

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ABSTRACT

Oncology drug development has seen a paradigm shift in the past decade from traditional cytotoxic agents to molecular targeted therapies. Given the different mechanisms and toxicities of these agents, drug development methodology may also require novel approaches. To address emerging issues in oncology drug development the 'Methodology for the Development of Innovative Cancer Therapies' (MDICT) task force was established to provide a forum for academic leaders involved in cancer drug development to discuss methodological issues inherent to the study of targeted anticancer therapy. At the inaugural MDICT meeting in 2006, discussion focused on the most appropriate primary endpoints for first-in-man phase I studies of targeted anticancer agents and organisational issues of such studies. This report summarises the scientific reviews and discussions as well as the recommendations regarding phase I trial design formulated by the MDICT task force.

1. Background

Over the past decade, there has been a significant shift within oncology drug development from traditional cytotoxic agents to therapies designed to affect specific molecular targets believed responsible for initiating or maintaining the malignancy. While the targets of cytotoxic drugs generally involve DNA, tubulin or other molecules involved in cell division, modern agents target specific proteins involved in such processes as cell signaling, oncogenesis or tumour suppression, cell cycle regulation, angiogenesis, immunologic pathways, metastasis and/or apoptosis.

It is not clear whether drug development principles that have evolved through the development of conventional

* *Corresponding author:* Tel.: +1 613 533 6430; fax: +1 613 533 2941.
E-mail address: eeisenhauer@ctg.queensu.ca (E.A. Eisenhauer).
[e] Research Fellow, NCIC Clinical Trials Group.
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chemotherapeutic agents, also apply in the modern era of targeted therapy. In addition to possessing differing mechanisms of action and antitumour effects, novel compounds may also display a differing spectrum of toxicity, or even a lack of toxicity, compared with conventional chemotherapy. In traditional phase I trials, toxicity is often the limiting factor in dose escalation. Because higher doses are generally expected to produce greater antitumour effects, toxicity has therefore been the traditional primary endpoint used to determine the recommended phase II dose. However, some investigators suggest that it may not be feasible (or appropriate) to consider toxicity as the primary endpoint for determining the recommended dose of novel molecular agents. Furthermore, demonstrating that a novel compound has the target effect for which it was designed may be an important aspect of early clinical development.

To address emerging issues in oncology drug development, the NDDO Research Foundation has established the 'Methodology for the Development of Innovative Cancer Therapies' (MDICT) task force as a forum for the discussion of methodological issues in contemporary oncology drug development. The mission of this independent international task force is to develop practical guidance on the optimal development of anticancer targeted agents as highlighted in Table 1. Membership in the MDICT task force is by invitation and includes a core group of academic drug development experts. Representatives from industry and regulatory agencies are invited to participate in the scientific session as observers.

The first meeting of the MDICT task force occurred on 15 March 2006 in conjunction with the 2006 International Symposium on Targeted Anticancer Therapies in Amsterdam. Participants included 23 experts from academic centres in 11 countries, together with 12 observers from industry and regulatory agencies. The mandate of the first MDICT meeting was to discuss and make recommendations regarding the most appropriate primary endpoints for first-in-man phase I studies of targeted anticancer agents. Dose escalation and starting dose for phase I trials were not considered. Two scientific presentations were followed by discussion involving all task force members and observers, resulting in the development of MDICT recommendations. These recommendations were reviewed and updated during the 2007 MDICT meeting on 7 March 2007 and by circulating a draft of this paper amongst task force members. While the initial discussion was related to appropriate endpoints, a number of other considerations important to phase I trials were discussed at this meeting and are included in this summary. The purpose of this report is to summarise the scientific presentations and task force discussion, and to present the 2006 MDICT recommendations.

Table 1 – Mission of the MDICT task force

The mission of MDICT is to develop practical guidance on the optimal development of innovative anticancer agents
1. Methodological guidance developed by MDICT should improve the efficiency of the future development of oncology drugs, in particular the early clinical phase
2. Output generated by MDICT should be generalisable to all targeted agents and not just confined to one drug class
3. Methodological output generated by MDICT should be made publicly available without restrictions on its use
4. Organisational aspects of early-phase clinical development of anticancer agents will be addressed to promote the smooth flow of the most interesting agents through the clinical development pipeline worldwide

2. Scientific review

2.1. *Is 'maximum tolerated dose' (MTD) a useful endpoint in phase I studies of targeted agents?*

Dr. Elizabeth Eisenhauer (National Cancer Institute of Canada Clinical Trials Group, Kingston, Canada) provided an overview of the goals of phase I oncology trials and what endpoints may be considered in the era of molecular targeted therapy. The primary goal of contemporary phase I trials remains the determination of a recommended dose and schedule for phase II study. Important secondary goals include a description of toxicity, pharmacokinetic (PK) and pharmacodynamic effects, and to describe any objective evidence of antitumour activity. Prior to implementing a phase I trial, preclinical data should ideally establish the molecular target of the novel drug, the effect of the drug on malignant (and normal) cells, and relationships between dose/schedule of the drug and antitumour effects, target effects, PK measures and toxicology. As shown in Fig. 1, pre-clinical information from each of these domains provides clinical investigators valuable insights regarding the starting dose for a phase I trial. The task force noted that 'maximum tolerated dose' (MTD) generally refers to 'recommended dose' in the United States, while in Europe and other jurisdictions it often refers to the dose level above the recommended dose.

The task force focused on two questions: (i) should the primary endpoint for phase I trials of targeted agents be toxicity?; and (ii) should phase II dose recommendation be the highest tolerable dose based only on toxicity? To address the first question the relative advantages and disadvantages of using toxicity as the primary endpoint in phase I trials were reviewed. Several of the reasons why toxicity is used as the primary endpoint in phase I trials of cytotoxic agents also apply to the development of targeted agents (Table 2): expected adverse effects must be defined for a new therapeutic agent; these adverse effects will ultimately direct dose escalation; and, toxicity may be mediated by target effects on normal tissues, such as those reported for agents targeting epidermal

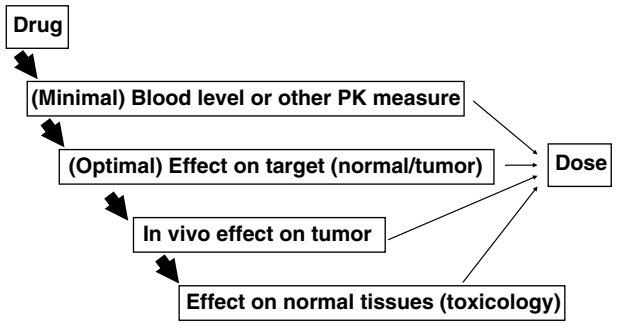

Fig. 1 – Ideal pre-clinical information for phase I trials of target agents.

Table 2 – Using toxicity as primary phase I endpoint: pros and cons

Pros	Cons
1. Toxic effects of new drugs must be measured, so a required component of trials in any case	1. Toxic dose: – may not be necessary – may not be optimal
2. Dose escalation will not proceed if toxic effects do not permit it	2. Toxic dose is not a sophisticated endpoint
3. Highest tolerable dose less likely to be too low	3. Toxicities may not be dose-related
4. Toxicity itself may be mediated by target effect	4. If toxicity is not target mechanism-based then may not guide dose selection (i.e. 'correct' dose may be different than maximally tolerated)

growth factor receptor (EGFR) (diarrhoea and skin toxicity) and VEGF (hypertension).[1,2] Conversely, if toxicity is not mechanism-based, it may not guide dose selection to find the most biologically active dose level.

Potential alternative primary endpoints for phase I studies include pharmacokinetic measures such as area under the curve (AUC), steady state or peak levels of drug in plasma and pharmacodynamic evidence of target inhibition in tumour or surrogate (normal) tissue. Although appealing from the perspective of rational drug design, the use of pharmacokinetics and/or pharmacodynamics as the primary endpoint(s) requires that a clear relationship exists between each of these variables and antitumour efficacy. Furthermore, both require the development of a validated assay, which can feasibly be applied to samples that are obtainable during the phase I study.

Results from a review of phase I methodology and endpoints were highlighted.[3] This overview included published abstracts and papers for 31 targeted agents, investigated in 57 phase I trials. The majority of trials halted dose escalation based on toxicity ($n = 36$). A phase II dose was recommended in 50 studies and in this subgroup, the dose recommendation was based primarily on toxicity (35 trials) or pharmacokinetic data (nine trials). Although toxicity remained the most commonly used endpoint and dose-determining variable, a substantial number of trials did evaluate alternative endpoints, including pharmacodynamic, laboratory and imaging studies. Tumour and normal tissue were evaluated in 5 and 15 trials, respectively, and imaging modalities were employed in 6 studies. Toxicity remained the most common determinant for halting dose escalation and defining dose recommendation for further studies.

In closing it was suggested that toxicity (e.g. MTD) and PK data appear to be reasonable endpoints to establish the dosing range for novel compounds. When molecular proof of principle is deemed important for subsequent development decisions, investigators should consider expansion of one or more cohorts after the conclusion of the escalation phase, or designing a separate study to confirm that the doses identified on the basis of toxicity or other means in fact are able to affect the molecular target.

2.2. *The use of biomarkers in phase I trials*

In the second scientific presentation, Professor Hilary Calvert (Northern Institute for Cancer Research, Newcastle upon Tyne, UK) provided an overview of biomarkers (here meaning pharmacodynamic measures of drug effect) in phase I trials.

Biomarkers include qualitative or semi-quantitative assays of tumour (indirect assays such as apoptosis or reduction in blood flow) or surrogate tissues such as peripheral blood mononuclear cells. Assays may be based on various methods including imaging, immunohistochemistry, or fluorescence *in situ* hybridisation. The development of an appropriate, accurate and standardised assay is critical for the successful application of biomarkers. Careful thought must be given to which tissue to use (normal and/or tumour) and when sampling of the tissue should occur relative to drug administration. The importance of having appropriate pre-clinical data demonstrating the effect of dose and PK (i.e. exposure, C_{max} and AUC) on target inhibition in normal and/or tumour tissue, efficacy and toxicology was emphasised.

Several examples of phase I trials, which incorporated biomarkers in their design were discussed. In one of the earliest uses of a biomarker, plasma oestrogen levels served as a marker of aromatase inhibition.[4] More recent studies have made use of a variety of other surrogate markers. Three particular examples were reviewed.

Plasma deoxyuridine has been used as a marker of thymidylate synthase (TS) inhibition in phase I trials of several agents including AG-337, raltitrexed and pemetrexed. Because the toxicity of TS inhibitors is exposure-dependent, several days of target inhibition was needed for biological activity to be manifest. In the phase I trial of AG-337, an initial 24-h infusion schedule was used to determine pharmacokinetics. Following this, plasma deoxyuridine was used as a surrogate marker for TS inhibition and, thereby, to determine a definitive dose schedule.[5]

The development of inhibitors of poly(ADP-ribose)polymerase (PARP) in combination with temozolomide provides an example of the use of another pharmacodynamic endpoint.[6] PARP is required for base excision repair and preclinical data suggest that inhibition of PARP will potentiate the antitumour efficacy of the alkylating agent temozolomide. Since PARP inhibition is not in itself expected to cause toxicity, an alternative endpoint was required to establish the dose of PARP inhibitors. Inhibition of PARP was measured in peripheral blood mononuclear cells until significant effects were seen, and then confirmed in tumour biopsy studies. While preclinical models in this example were useful, it was noted that neither the extent of inhibition nor the duration required for optimal effect could be reliably predicted from preclinical data.

Direct measurement of target effects in tissue was used in the development of the EGFR tyrosine kinase inhibitor, gefitinib. In a phase I study of gefitinib, 84 of 88 patients with five tumour types were given the drug at 225–1000 mg/day orally.[1] Skin biopsies were obtained from 42/88 patients and pharmacodynamic studies yielded impressive target effect results. Although overall EGFR expression in skin biopsies did not change, a significant reduction in the expression of *activated* EGFR (phosphorylated) and *activated* mitogen-activated

protein kinase (MAPK) was seen following initiation of gefitinib treatment. It is unclear whether inhibition of the target in skin bears a relationship to inhibition in tumour, and also whether these data influenced the choice of dose for subsequent phase II and III studies.

Several potential roles for biomarkers in phase I trials were proposed: (a) as a study endpoint in phase I trials (assuming there is sufficient pre-clinical data concerning the biology of the agent, the target and the effector system of the target); (b) as part of a 'hybrid' design, as exemplified by the PARP inhibitor study; (c) confirmation of target effect in a clinical setting where it may be correlated with observed (or lack of) therapeutic effect; and (d) as a key component in deciding whether to progress to phase II development. Concerning the latter point, the decision to move an agent forward to phase II development in the *absence* of any observed target effect in phase I remains a challenge.

Professor Calvert's recommendations to the task force were that phase I trials of targeted agents establish a dose range with the upper limit defined by toxic effects. In the absence of toxicity, one could consider biomarker measurement (tissue-based or imaging), pharmacokinetic measurements and/or dose and schedule feasibility. Before making a final decision on dose it was suggested that other important inputs be considered, including: clinical proof of principle (target effect), clinical antitumour effect and PK data. Such additional inputs may require a new trial or accrual of an expanded cohort in phase I.

3. Design and organisation of phase I trials

During the discussion following the scientific presentations, the task force considered not only the issue of phase I endpoints but also reflected on the overall design, planning and output of phase I trials of targeted anticancer agents.

3.1. *Design and planning of phase I trials*

Although it is not always the case that pre-clinical data on novel compounds provide information regarding the relationships of target–effect and dose–effect on antitumour efficacy, members of the task force nonetheless felt when this was available it was very important to consider the impact of these data when designing a phase I trial.

Phase I investigators experience increasing pressure to include large numbers of laboratory and imaging studies as obligatory components of phase I trials in situations where the results of these procedures have not been shown to be useful or validated in pre-clinical work. Considerable discussion ensued regarding the mandatory inclusion of biomarkers as endpoints in phase I trials. It is important to distinguish between what is '*necessary*' to know in order to decide what dose to recommend for further study versus what would be '*desirable*' to know and define the endpoints and procedures of the study accordingly. Inclusion of biomarker studies (pharmacodynamic measures) should not be 'routine'; rather this should be based on clear information from the preclinical setting on their value in dose selection.

Biomarkers that are not yet shown to be of value in preclinical models and for which a robust hypothesis does not exist should be refined in the lab during a dose-ranging phase I trial and then considered for inclusion in *later* studies using the recommended dose, rather than in first-in-human trials. Phase I studies should not mandate hazardous, time-consuming or uncomfortable procedures unless the assay for the biomarker has been validated and its outcome will play an important role in the interpretation of the study outcome.

It was recognised that the dividing line between which assessments are '*necessary*' versus those that are '*desirable*' may be difficult to judge. For a drug that is first in class, proof of concept studies may be an important (and perhaps essential) component of a phase I study. Demonstrating target effect may not be so critical for subsequent analogues in the same class.

3.2. *Output of phase I trials*

Participating phase I investigators must have access to all data emerging in the course of the trial, including clinical, pharmacokinetic and pharmacodynamic data, in order to provide input into the analysis and interpretation of the data.

In addition to defining dose of a new drug given in a particular schedule, it was noted that phase I trial results may be required for making stop/go decisions for the continued development of a targeted agent. Data from phase I trials may also guide the design of subsequent studies by suggesting new treatment schedules, or may direct which disease-specific studies are undertaken in subsequent development based on early signs of activity.

A topic that was widely discussed was the desirability of defining the 'biologically active' dose range especially for agents likely to be combined with other agents, which may limit dosing of the targeted agent if there is overlapping toxicity. This may be done most effectively in an expanded cohort or a separate dose ranging pharmacodynamic study. It was recognised that the definition of the dose ranges to be studied in such a biomarker study (other than the highest one defined by toxicity) requires careful evaluation of all available pre-clinical and clinical data including pharmacokinetics.

Finally, in interpreting the results of a phase I trial it was felt that one should make a clear distinction between the observation of the desired molecular effect of drug (i.e. proof of concept) and the impact of the drug treatment on clinical measures such as tumour shrinkage or delay in progression (i.e. clinical benefit). Although tumour response is not normally a primary endpoint in phase I trials, evidence of molecular target effects in subsets of phase I patients may assist in defining which predictive biomarkers and assays are worth investigating further in phase II studies.

4. MDICT task force recommendations

Based on the scientific presentations and the subsequent discussion, the MDICT task force prepared an algorithm (Fig. 2) and a series of recommendations for the design, implementation, analysis and output of first-in-man phase I trials of targeted agents.

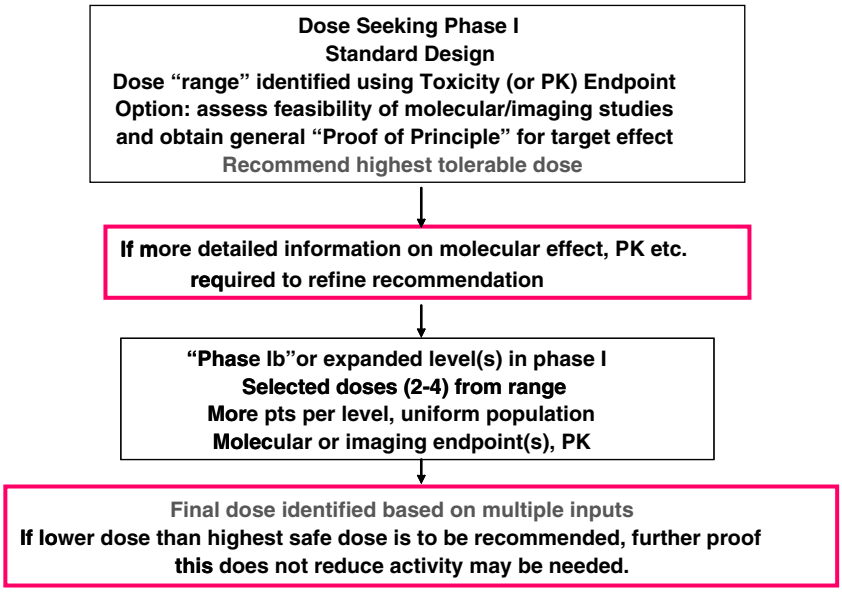

Fig. 2 – Proposed phase I algorithm for novel molecular compounds.

4.1. *Design and planning of phase I trials*

1. Pre-clinical studies should provide information concerning dose, schedule and PK effects on:
   (a) Target effect in normal and/or tumour tissue.
   (b) Antitumour efficacy and the minimal level and duration of target effect required to achieve this.
   (c) Toxicological effects.
2. In designing the phase I protocol, investigators should establish what they *need* to know to define the recommended dose and to continue development of the drug. These criteria should be pre-specified.
   (a) Any planned proof-of-concept/biomarker assays should be developed and fully validated before the start of the phase I study.
   (b) Unless deemed necessary (i.e. for first-in-class), such studies should preferentially be undertaken in patients enrolled at potentially therapeutic doses and may be helpful in establishing a 'biologically active' dose range.
3. Care should be taken not to mandate hazardous/uncomfortable procedures unless validated and essential to the endpoint of the study.
4. Appropriate communication channels must be in place to ensure that all investigators have real time access to emergent data irrespective of whether multiple institutions are participating. Single centre or limited centre participation is strongly recommended.

4.2. *Implementation and analysis of phase I trials*

5. Establish dose range with the upper limit defined by toxic effects. It was generally agreed that toxicity remains a useful measurement to establish dose range. This is particularly true if toxic effects are mechanism-based.
6. If no toxic effects seen, other factors to consider include:
   (a) Biomarker measurements: tissue-based or imaging. Caution should be used in interpreting such data because visually dramatic changes in images or immunohistochemistry results can still reflect a biological change of an insufficient magnitude to have an antitumour effect.
   (b) PK measure(s) (for example AUC, time above a threshold or steady state concentration, depending on what is known about the mechanism of action of the drug).
   (c) Feasibility of delivery of the dose.
7. In the absence of a clear biological rationale to suggest otherwise, it was concluded that the recommended dose will be the *highest safe dose*.
8. Before a final decision on the recommended dose is made, review other inputs:
   (a) PK data: Are minimum or target concentrations achieved in plasma and/or tissue (taking account of protein binding)?
   (b) Antitumour activity: Is there any evidence of an antitumour activity? If so, is there evidence of a relationship to dose?
   (c) Proof of concept data (if planned): Is the drug having the intended molecular effect? In relevant tissue? Is this dose-related? Does it achieve minimum target effect level? Generating these data may require a new trial or expanded cohorts within the phase I study.

4.3. *Output of phase I trials*

9. Investigator involvement in the design and conduct of the study and in the interpretation of the data are paramount and investigators should have full access to the source data of any pharmacokinetic or pharmacodynamic studies.
10. Upon completion of the phase I trial there should be clear conclusions regarding:

(a) Phase II dose recommendation.
(b) If future combination studies are planned, a range of doses, which appear to be biologically 'active' should be defined.
(c) Go/No Go decision for further development, if applicable, should be made based on achievement of prespecified criteria.

5. Summary

Oncology drug development has seen a paradigm shift in the past decade from traditional cytotoxic agents to molecular targeted therapies. Given the different mechanisms and toxicities of these agents compared to conventional chemotherapeutic agents, drug development methodology may require novel approaches. In an effort to address this issue the MDICT task force was established as a forum for academic leaders to discuss methodological issues inherent to the development of targeted anticancer therapy. Although starting dose selection and dose escalation strategy are important topics in anticancer drug development, defining appropriate endpoints for phase I trials was the focus of the first MDICT task force meeting. Current practice suggests that toxicity remains the most commonly used information upon which decisions are made for the recommended phase II dose of targeted agents. Although there remains strong rationale for the use of toxic effects, investigators and sponsors should also consider other inputs including biomarker effects, pharmacokinetic endpoints and antitumour activity in determining the recommended dose of a novel molecular compound. Future meetings for the MDICT task force are planned and will review phase II design, phase 0 studies and other topics of interest.

Conflict of interest statement

None declared.

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