

Design of Phase I and II Clinical Trials in Oncology and Ethical Issues Involved

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Abstract

Introduction: There are 2 broad classes of anticancer drugs that require different approaches to development. The classical cytotoxic agents have low therapeutic indices and therefore traditionally have different developmental strategies from non-oncology agents. The newer anticancer agents that target the signal transduction pathway and antiangiogenesis pathway have characteristics similar to non-oncology agents and will change the paradigm for drug development in oncology. **Methods:** To review the issues involved in phase I and II cancer trials, and to describe how these issues have been addressed. **Results and Conclusions:** There are significant scientific and ethical issues in phase I and II cancer clinical trials, which influence the design of these studies. Nonetheless, these trials are vital for the successful development of anticancer agents. The development of novel anticancer agents that target signal transduction and antiangiogenesis has posed great challenges, and changes in the conventional cytotoxic paradigm of development are expected for these agents.

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Introduction

Drug development is costly and time-consuming in terms of economic, patient and research resources.¹ An integrated effort involving academia, industry, and regulatory authorities is needed to ensure novel, effective therapies continue to be approved for clinical use. Conflicts of interest exist between these parties in the drug development process. The pharmaceutical industry is under pressure to develop drugs rapidly for approval for various indications. On the other hand, regulatory authorities mandate clear guidelines for safety and efficacy during the testing of novel therapies. Patients who are eligible for clinical trials largely participate for expected benefits that they often perceive to be higher than their physicians do. Physician researchers involved in drug development have an ethical obligation to provide the best treatment for their patients but yet fulfil the scientific requirements of the clinical trial protocols. These issues determine the processes involved in the early phases of clinical drug development, and the design of phase I and II clinical trials, and will form the focus of this paper. Recognising that it is impossible to encompass all issues in a review like this, the article will focus on several more salient features of phase I and II clinical trials in oncology.

Phase I Clinical Trial

The phase I clinical trial is the first evaluation of a drug in humans and is therefore the gateway to the development of the drug.² It answers the questions relating to the:

- Maximum tolerable dose (MTD) of the drug in humans
- Toxicity profile of the drug
- Preliminary data on the pharmacology of the drug
- Preliminary evidence of an antitumour effect³

Cytotoxic drugs have low therapeutic indices and therefore propensity to cause toxicity at clinically relevant doses. Thus, the traditional design of a phase I cancer clinical trial begins with treatment at a low dose that is considered safe in humans, and small patient cohorts are treated at each dose level, with cautious dose escalation steps till a defined toxicity endpoint is reached. The traditional design employs a starting dose that is 1/10th of the dose (in mg/m²) that is lethal to 10% of mice treated (LD10) or one-third the minimum dose that causes any toxicity (TDL) in dogs (whichever is the more sensitive species). A small cohort (usually 3) of patients is then treated, and the toxicity experience is used to determine the safety for dose escalation to the next dose level, and so on. Usually a modified Fibonacci series (Table I) is used to guide dose escalation, and cohorts of 3 patients are treated

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TABLE I: MODIFIED FIBONACCI SERIES

Multiple of starting dose	% rounded off increase above previous dose level
1.0	100
2.0	67
3.3	50
5.0	40
7.0	30-35
9.0	30-35
12.0	30-35
16.0	30-35

at each dose level. If one patient develops dose-limiting toxicity, the cohort of patients will be expanded at that dose level. Usually the maximum tolerated dose is exceeded at the dose where one-third or more patients develop dose-limiting toxicity.^{4,5}

This classical design has been used for many years and therefore has been “time tested” to be usually safe. However, there are many drawbacks of this traditional phase I trial design. Though its safety record is quite well accepted, often a considerable drain of resources results from too many dose escalation steps needed to reach the MTD when using such a rigid, inflexible design. The starting dose may be viewed as empirical and conservative; the dose escalation process has little scientific rationale, and requires too many steps that exposes a fair number of patients to low and presumably ineffective doses of treatment.⁶

Starting Dose

The starting dose is chosen to avoid exceeding the maximum tolerable dose based on preclinical animal toxicological studies. If the drug metabolism of the preclinical species studied and humans differ, problems may arise in using this empirical approach to assign a safe dose in humans. Indeed, differences in metabolism are known to exist. For instance, rats are not a good species on which to base starting dose recommendations for thymidylate synthase inhibitors since they have a high serum level of thymidine, which bypasses the inhibition of thymidylate synthesis through the salvage pathway.⁷ For this reason, the dog was used to determine the starting dose of the specific thymidylate inhibitor developed by AstraZeneca, ZD9331.⁸

Application of *in vitro* and *in vivo* preclinical pharmacokinetic data and allometric scaling to predict *in vivo* drug clearance in humans would be of value in determining a safe starting dose that is based on scientific rationale and may be less conservative (Fig. 1).^{9,10} Allometry is the study of relationships between body size and the structure or functional capacities of organs.^{11,12} It allows the

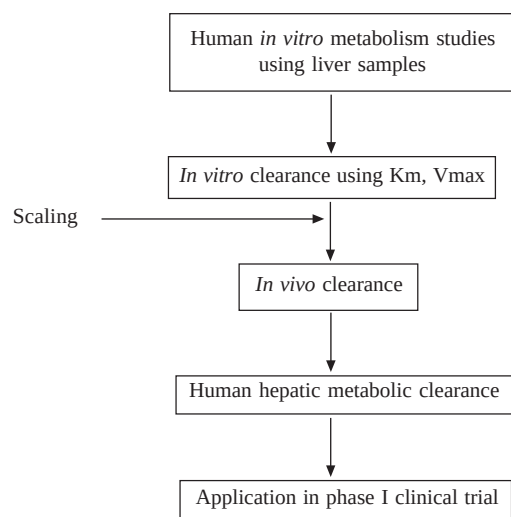


Fig. 1. Allometric scaling for extrapolation of *in vitro* and *in vivo* preclinical studies to predicting *in vivo* human clearance.
Vmax: maximum rate of metabolism; Km: Michaelis-Menten constant

extrapolation of animal data to predict pharmacokinetic parameters in humans. *In vitro* human metabolism data using liver tissue can allow prediction of *in vivo* human clearance through scaling or correlation analyses. Empirical and physiologically based methods exist to combine these 2 approaches for better performance. Currently, allometric scaling with *in vitro* human data and *in vivo* preclinical data can predict *in vivo* human clearance within a two-fold factor of actual human values 80% of the time. More accurate predictions will be made possible using physiologically-based approaches using data from a pool of human liver samples, as interindividual variability can be addressed. Certainly this should be explored further in future in the development of anticancer drugs.^{13,14}

Dose Escalation

There is no ideal way to dose escalation. It is an exercise of optimisation to ensure that ethical, scientific and economic concerns are addressed. Dose escalation has been the main focus of efforts to improve the design of phase I studies. The “up and down” designs involve treating single patient cohorts, rapid escalation for no DLT observed, and de-escalation for DLT observed.¹⁵ These designs differ from the traditional design in that they allow for more flexible rules for dose escalation and de-escalation, single patient cohorts, and varying percentage of dose escalation depending on the severity of toxicity. The advantages of this approach are that rapid escalation is achievable, and most patients would be treated at doses that are around the middle of the dose-range. Two-stage designs were proposed by Storer based on the “up and down” approach, where initial dose escalations involved single patient cohorts until

toxicity was seen, at which point stage II continued with de-escalation to the next lower dose and treatment of subsequent dose cohorts with larger sample sizes. Compared to the single stage approach in a steep, medium and shallow dose-response curve simulations, the two-stage approach allowed less bias in determination of the maximum-tolerable-dose and allowed a higher proportion of patients treated at higher doses.¹⁶ Some criticisms of the phase I trial designs are that they do not fully utilise the toxicity experiences of patients in deciding how to escalate the dose and focus on only the first 1 or 2 cycles without consideration of cumulative toxicity. Simon et al¹⁷ proposed using rapid inpatient dose-escalation in the early phases of the study until some toxicity (one patient with DLT or 2 with grade 2 toxicity) at which further dose cohorts used 3 to 6 patients and progressed at 40% dose escalation steps. Inpatient dose escalation allowed a greater chance for patients to receive clinically meaningful doses of agents for response. This accelerated titration design also reduced the number of patients required for the trial, and shortened the length of the study.

Model-based approaches attempt to utilise dose-effect information available to develop models to predict the MTD. Dose escalation is then based on the predicted dose and more information obtained from treatment can be incorporated into the updated model, and the iterative process goes on. An example of this is the continual reassessment model which uses Bayesian theory.¹⁸⁻²⁰ The process begins with determining the priors, i.e. the information that can be used to derive the dose-effect relationship. These parameters may be derived from preliminary data or from investigator knowledge. They have distributional characteristics that must be assigned (the prior distribution). A mathematical dose-effect model is then used to fit the priors. The target toxicity is then selected and an estimated dose that gives this target toxicity is used to treat a patient. The resulting toxicity information is then used to update the model; based on this model, the new estimate of the dose that will give the target toxicity is used to treat another patient, and so on. This method obviously allows more patients to be treated at doses closer to the MTD, and makes use of known toxicity information to make decisions on dose escalation. However, the method is very much dependent on the priors, and may potentially expose more patients to dose-limiting toxicities. This method has been applied to the development of several antineoplastic agents. An example is 9-aminocamptothecin, where theoretical comparison to the conventional dose escalation methods suggested significant savings in terms of patient resources.²¹ A modification of this approach was proposed by Faries, where a number of controls to the dose assignment step was introduced to reduce the risk of excessive toxicity.^{22,23}

Another model-based approach utilises dose-adaptation, where information gained from the early phase of conventional dose escalations is utilised to build a pharmacodynamic model of toxicity, using neutropenia or thrombocytopenia. Ratain et al showed that this method resulted in more precise identification of the MTD and with less patient resources.²⁴

Pharmacologically based dose escalation (PGDE) was proposed by Collins et al based on the observation that the drug concentration-time product or the area-under-the-concentration-time curve (AUC) of mice at the LD10 was similar to the drug concentration-time product or AUC of patients treated at the MTD in an analysis of 13 phase I clinical trials.^{25,26} The LD10 was not similar to the MTD in many trials. He therefore proposed a rapid escalation (either doubling or using geometric mean) of the dose of drug in each patient cohort beginning from the starting dose with comparison of patients' plasma AUC with mouse AUC at LD10 until the dose reached within 40% of the target AUC, at which point further dose escalations proceeded more cautiously in smaller steps. Simulations showed that this method could significantly reduce the number of dose escalation steps required to reach the MTD. Several requirements for such a design include the need for a sensitive and specific assay, linear pharmacokinetics (to allow prediction of the expected MTD), similarity of protein binding and drug metabolism between the mouse and human species and good correlation between the AUC and toxicity.^{27,28} In addition, the presence of active metabolites in one species compared to the other would complicate applicability, as in the case of iododoxorubicin, where the presence of an active metabolite iodo-doxol in man but not in mice led to difficulty in initial application of PGDE.²⁹ Wide interindividual variability of pharmacokinetics may also discourage the use of this design, as in the case of the anthrapyrazole losoxantrone (Dup-941).³⁰ For reasons of assay insensitivity, PGDE in the microtubule toxin rhizoxin was also not feasible.^{31,32} Therefore, although PGDE is highly interesting scientifically and applies both preclinical and clinical pharmacokinetic data, it is not applicable to all situations.

Statistical Issues in Phase I Clinical Trials

The objective of collecting toxicity data from patients at each dose level is to define the population distribution curve of each toxicity at each dose level. The larger the sample at each level, the more accurately the data will statistically reflect the toxicity of the dose level.³³ Given the limited number of patients initially treated at the MTD, wide confidence intervals of the MTD is a problem that has been highlighted. Therefore it is recommended that more patients (e.g. 12) be treated at the MTD.

Dosing of Cytotoxic Drugs

At this point, it may be relevant to consider the fact that given the great effort involved in the determination of the MTD of anticancer drugs, the degree of interpatient pharmacodynamic variability remains a considerable problem in routine clinical practice. More work is required during the dose-finding stage to explore ways to refine dose recommendations based on more defined individual predictors than on body surface area alone.³⁴⁻³⁶ Carboplatin dosing using the Calvert formula is an example of how this can be achieved, based on the understanding that carboplatin is primarily cleared by renal mechanisms.³⁷ Recently the role of polymorphisms of drug metabolising enzymes in determining interpatient variability of pharmacokinetics and pharmacodynamics has been elucidated for many drugs.^{38,39} Using the antimetabolite mercaptopurine as an example, Relling et al showed that genotype of the metabolising enzyme thiopurine methyltransferase (TPMT) was a good determinant of its toxicity. Children with acute lymphoblastic leukaemia who received standard doses of 6-mercaptopurine could be divided into 3 groups according to their TPMT genotype of homozygous wild type, heterozygous, and homozygous deficient. These correlated well with tolerance of therapy, with the homozygous deficient developing most serious toxicity, followed by the heterozygotes.⁴⁰ Other enzymes like dihydropyrimidine dehydrogenase for 5-fluorouracil,⁴¹ N-acetyltransferase for amonafide,⁴² uridyl diphosphoglucuronyl transferase 1A1 for irinotecan have also shown clinically significant polymorphisms.⁴³ Given its significance in prediction of toxicity, pharmacogenetics is poised to play an important role in individualising drug dosing, and will be studied early in drug development. *In vitro* techniques using human liver tissue to predict human *in vivo* drug metabolism of anticancer agents may allow application of genotyping or phenotyping (using an appropriate probe drug) enzyme activity prior to dosing.⁴⁴ In such situations, a valid definition of the MTD in a phase I study may be in terms of a formula that incorporates individual patient characteristics and metabolising enzyme genotype or activity rather than in mg/m².

Ethical Issues in Oncology Phase I Trials

The potential for significant toxicity resulting from treatment with oncology agents puts ethical constraint against testing the agents in normal healthy volunteers. The low expected response rate (4.2%), and the fact that the primary objective of a phase I study is not tumour reduction further increases ethical concern for the reason to conduct phase I clinical trials, as it seems to contravene the Principle of Beneficence as stated in the Belmont report, as well as the Hippocratic Oath which states “the health and life of my patients will be my first consideration”. However, the

counter arguments hold sound that without these “gateway trials”, we would not make much progress in the treatment of cancer. In consideration of the Principle of Beneficence, the Belmont Report also states “that we be concerned about the loss of the substantial benefits that might be gained from research”. In a phase I cancer study where patients have incurable tumours refractory to standard treatment, even a few patients who benefit may justify conducting the trial, as long as the foreseeable risks of injury are kept minimum by careful consideration to study design.⁴⁵ In addition, patients who participate in phase I studies may derive psychological benefit, though this may be difficult to quantify.

Empirical survey studies revealed that most patients participating in phase I cancer trials did so with anticipated therapeutic benefit. Daugherty et al at the University of Chicago conducted a survey using a questionnaire study and interview process to understand the differences in perceptions and attitudes of patients with refractory cancer participating in phase I clinical trials and their oncologists. Eighty-five per cent of patients participated in phase I trial because of possible benefit. Altruism was a minor reason for participation.⁴⁶ Of concern was the fact that only 33% of patients were correctly able to describe the purpose of the phase I study as dose-finding studies as explained to them during the informed consent process, despite 90% of these patients giving a positive response to the question on their understanding of the purpose of the phase I trial. Given these findings, it appears that the written informed consent provides limited patient understanding of the purpose of a phase I oncology clinical trial.⁴⁷ Clearly more needs to be done to understand the ethics of the informed consent process of a phase I trial, and the decision making processes involved in determining trial participation.^{48,49} Despite all these ethical concerns, phase I oncology trials should continue to play a major role in the development of improved treatments. Trial designs should seek to reduce patient risks, and patients should be clearly informed of trial objectives, foreseeable risks and possible benefits before their participation.

Pharmacological Studies in Early Phase Clinical Trials

The purpose of studying pharmacology during drug development is to elucidate dose-concentration-effect relationships, which may facilitate the drug development process, or improved clinical use of the drug. Pharmacokinetic and pharmacodynamic data should be collected throughout the phases of drug development.⁵⁰ Phase I trials provide the only opportunity for studying the pharmacokinetics of a drug in the setting of wide dose-ranging studies, and yield valuable data on the pharmacokinetic characteristics of the drug, like linearity. The small sample size of patients treated at each dose level

limits the application of population approaches, but full pharmacokinetic sampling of each patient involving more than 10 samples is feasible, and provides rigorous data on the individual concentration-time curves. Phase II studies involving larger numbers of patients treated with the same dose of drug and with homogenous characteristics are the setting for pharmacokinetic studies that study the cause of interindividual pharmacodynamic variability. These studies usually involve more sparse sampling points per patient for patient convenience and to simplify logistics.^{51,52} To do so requires a validated limited sampling strategy based on the data collected from the phase I studies. Two approaches to this are commonly used; the limited sampling methods based on relatively simple linear regression analysis, or limited sampling based on the optimal sampling theory.^{53,54} The data obtained from many patients can then be used to study population pharmacokinetics and pharmacodynamics.⁵⁵

Phase II Trials (Fig. 2)

Phase II clinical trials answer the question of whether a new drug, new schedule, or new drug combination has sufficient efficacy in a limited sample of patients to merit further evaluation in a randomised phase III trial that is expensive in terms of patient, time and economic resources. They are usually single-arm studies involving about 35 to 50 patients who are homogenous for tumour type, organ function and treatment dose. The endpoints of such a study include the rate of partial and complete response, the time to treatment progression, and the toxicity profile. It is

important to realise that phase II studies test a surrogate endpoint of tumour response rate, which does not necessarily correlate with overall survival. Given this, a significant endpoint in a phase II study should include quality-of-life assessments (QOL). For example, in advanced pancreatic cancer, gemcitabine was approved for first-line use based on QOL improvement over 5-fluorouracil in a randomised phase II study.⁵⁶ Recognising that prolonged tumour stabilisation may be as relevant as tumour shrinkage to the patients, another endpoint likely to be of increasing significance is the time-to-progression. Interleukin-2 was approved for use in renal cell carcinoma based on phase II studies despite the low response rate of only 15% because durable responses of about 5% were observed.⁵⁷⁻⁵⁹

Issues in the Design and Conduct of Phase II Clinical Trials

Phase II clinical trials of the same anticancer treatment often have great variability in the reported response rates. Some factors that may account for this variability include patient selection criteria, subjectivity of assessing response, differences in the dose modification recommendations and protocol compliance, differences in reporting responses and statistical unreliability of conducting a trial with a small sample size. More heavily pretreated patients are less likely to respond to chemotherapy, and enrolling them in phase II studies together with chemo-naïve patients would lead to complexities in interpretation of response rates. In addition to the increasing chemo-resistance, prior therapy often results in less tolerance to chemotherapy and therefore

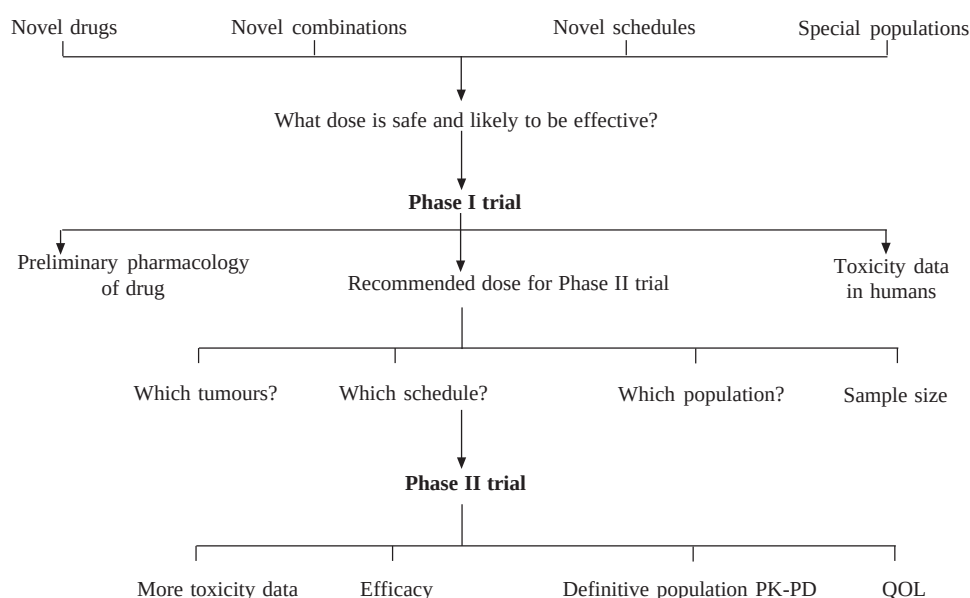


Fig. 2. Issues in phase I and phase II clinical trials.

heterogeneity in dose intensity. Inter-observer bias may be reduced by independent review of response rates by external observers.⁶⁰ Some of these problems in phase II studies may be reduced by randomisation as proposed by Simon (see below). Additionally, several phase II studies of the same drug should be conducted at different centres even though one trial has shown it to be inactive, as this will reduce the problems which are associated with patient selection, inter-observer bias and lack of uniformity of treatment.

Randomised Phase II Trial Designs

Randomised phase II studies are interesting in design and provide more useful information in some situations.⁶⁰ The number of patients involved is smaller than a phase III study. The selection theory is utilised to select the treatment that is superior in response rate to another by a defined amount. This approach allows the superior treatment to be selected with a high probability, regardless of the significance level of the difference. There are advantages of this phase II trial design in situations where there are several experimental therapies available for testing or several schedules of a same drug. Deciding which schedule of a novel agent to use after several phase I studies of different schedules have been completed will pose a problem, especially if both have similar toxicity profiles, show some activity, but yet use different dose intensities. Pushing for the schedule with higher dose intensity would be the obvious choice from the pharmaceutical point of view and this has scientific basis from the point of maximising chances of response. However, if the other schedule is subsequently proven to be as effective after the drug has been approved for marketing, the pharmaceutical sponsor may face a situation of reduced drug usage and therefore revenue loss. Gemcitabine (Gemzar®) is a nucleoside analogue which may have benefited from more detailed analysis of the schedules of administration.⁶¹ The weekly short 30-minute infusion was approved for use, and it was apparent from the early phase II trials that the dose could be escalated considerably without compromising safety.⁶² Elegant studies evaluating the active intracellular metabolites demonstrated that the intracellular activating enzyme, deoxycytidine kinase, was the rate limiting step in the activation of gemcitabine.⁶³⁻⁶⁵ Excess drug given beyond the saturation level of this enzyme was deactivated by cytidine deaminase. In a randomised phase II study in advanced pancreatic cancer, the prolonged infusion of gemcitabine (150 minutes versus 30 minutes), guided by pharmacological principles of saturating intracellular deoxycytidine kinase, was shown to result in significant improvement of response and increased intracellular concentrations of activated gemcitabine metabolites.⁶⁶

Tumour Assessment

Response measurement in cancer trials utilise bidimensional measurements of measurable lesions defined by 2 measurable dimensions are evaluated for tumour response.⁶⁷ Problems still exist in the assessment of some tumours that are less measurable, like prostatic and pancreatic cancer. In such tumours, serum tumour markers like the prostatic specific antigen and the CA-19-9 have been used in clinical trials, but there are inherent problems with these, as there is generally a lack of validation of these tumour markers as surrogates of tumour response.

Recently, there has been a move towards using unidimensional measurement for tumour assessment. It was observed that bidimensional measurements resulted in variations in the tumour assessment and definition of progression in the setting of multiple lesions, and the advent of CT scans and MRI led to the possibility of 3-dimensional measurements and therefore more variability in response assessment. Therefore, unidimensional assessments were studied in comparison to bidimensional assessments in 14 trials and no difference in the percentage of responders was found. The authors recommend that this set of criteria based on unidimensional measurement, Response Evaluation Criteria in Solid Tumours (RECIST) be utilised for tumour response assessment.⁶⁸

Reporting of Results

Phase II clinical trials often report the overall response rate by the number of complete and partial responses out of the evaluable patients. As tumour response is often based on completion of 2 cycles of treatment and repeat radiological assessment a month after to confirm response, a proportion of patients would be inevaluable through toxicity or other reasons. The reporting of overall response rate should include both the evaluable patients and all enrolled patients. Both figures give important information on the activity and the tolerability of the experimental treatment.

Sample Size

The sample size of a phase II clinical trial is an issue that has received considerable attention. In a phase II study, the risk of no response in a patient treated is counterbalanced by the risk of discarding a potentially efficacious treatment due to non-responders in the treatment of the first few patients. Therefore statistical methods have been applied to control for false positive (accepting an ineffective treatment) and false negative (discarding an effective treatment) errors that may be incurred in conducting a phase II trial.⁶⁹ The classic Gehan's design is a 2-stage design to provide for early stopping if the response rate in the first stage. For instance, if the response of interest is

20%, then the first stage will include 14 patients. If no responses are seen, then the treatment is discarded with a false negative error of 4% such that the true response rate is less than 20%. However, if 1 or more responses are seen, then the accrual will continue to the second stage, the sample size depending on the standard error one is willing to accept.⁷⁰ Modifications to this design include Fleming's multistage design that allows early stopping for early stage response rates that reach a prespecified level of interest.⁷¹ Other designs like the Simon Minimax design, Ensign's design and Sylvester-Staquet design have been proposed.⁷²⁻⁷⁴ A detailed discussion of these designs is beyond the scope of this paper. Reviews of this topic have been published.^{75,76} From the patients' viewpoint, the designs of phase II studies based on statistical argument alone may be questioned. A review of the phase II cancer trials conducted at the NCI by Marsoni et al⁷⁷ showed a low average response rate. The other less well considered fact is that a higher percentage of patients in phase II studies are treated at higher doses and therefore a higher rate of toxicity is seen compared to phase I trials. Therefore, ethical concerns of possible cost to the patient in terms of toxicity, versus the low likelihood of therapeutic gain have to be addressed. To the patient, the early stopping rules may not be acceptable. Patients may not want to be the 14th patient to enrol on the study, if they were made aware that the first 13 had not responded.⁷⁸ Patients may wish to know the number of previous patients accrued to the same study who have responded, which is currently not uniformly included in the informed consent process. A dynamic consent form that updates the response and toxicity results of the study as it continues to accrue patients may address this issue. At the University of Chicago, a study was conducted to examine these issues. Using semi-structured interviews of patients enrolling on phase II cancer trials in the institution, 55% of patients were able to define a threshold number of non-responders that would stop them from enrolling on the study. The median number was 5 (range 1 to ≥ 99). Eighty-six per cent said they would like information on how previous patients on the investigational therapy had fared, with 64% who felt this information should be put in the consent form.⁷⁹ From a physician's perspective, when does a trial accruing patients who do not respond to treatment reach a stage that most clinicians feel it is unethical to put a patient on the study with no expected benefit?

Development of Drugs Targeting Signal Transduction and Antiangiogenesis

As mentioned, these agents provide basis for the paradigm shifts associated with the early phase development of anticancer agents.⁸⁰ Examples of these agents include the inhibitors of the epidermal growth factor receptor (EGFR) like cetuximab (monoclonal antibody) and ZD1839 (small

molecule), farnesyl transferase inhibitors, and antiangiogenic agents like SU5416 (small molecule) and endostatin. They differ from cytotoxics in several ways: they are likely to have more favourable toxicity profiles, their mechanism of action is cytostatic, they would probably be developed for chronic administration, and oral administration is the probable route of administration.⁸¹ In developing such agents, we would need to re-examine current phase I and II cancer trial design. It may no longer be appropriate to use tumour shrinkage as a measure of antitumour activity, since these agents may inhibit tumour progression for prolonged periods with minimal toxicity. It would be necessary in developing these agents to bear in mind the following principles:

1. Prove that the agent acts by the described mechanism.
2. Prove that the agent has antitumour activity *in vivo*.
3. Prove that the antitumour activity is due to the described mechanism of action.

These agents have similarities with non-oncology drugs which are used to treat chronic diseases, where maintenance administration is needed for disease suppression, and no easily measurable pharmacodynamic endpoints may be apparent. On the other hand, during phase I clinical trials, it would be necessary to demonstrate inhibition of their specific molecular targets. The endpoint of phase I dose-escalation studies should therefore be an optimal dose that inhibits a relevant molecular marker, and not the MTD. Other key endpoints would include safety data and plasma and intracellular pharmacokinetic-pharmacodynamic data. These pharmacological data are important to help determine the dose, schedule of these agents and to increase understanding of their clinical use. In determining this optimal dose, various surrogate markers have been suggested, like measurement of the molecular effects of treatment with preoperative and postoperative tumour biopsies or in more easily accessible peripheral mononuclear cells, or positron emission tomography or magnetic resonance imaging, which may be of relevance to antiangiogenic drugs.⁸² In phase II trials, the key objective is to demonstrate that the drug does have clinically relevant antitumour activity to merit commitment of more resources in larger studies. Tumour response in terms of shrinkage of the tumour may not be the appropriate endpoint; time to progression, quality of life measures would be clinically more relevant and arguably reflect more direct benefit to the patient. The problem then is to find an appropriate control group that is not treated, since single arm studies as in conventional single-arm oncology phase II trials would be difficult to interpret with respect to these endpoints. Randomised phase II trial designs (see above) may be appropriate, e.g. comparing drug + conventional cytotoxic versus cytotoxic alone. In the case of ZD1839, an oral small

molecule against the EGFR, its developers AstraZeneca has made the decision to proceed directly to large definitive randomised phase III studies in non-small cell lung cancer comparing ZD1839 + cytotoxic versus cytotoxic alone. Despite the adoption of the above design, it does not prove that the drug has antitumour activity by itself. Another study design, comparing drug versus no drug may be a problem for patient acceptance to justify no treatment for a progressive condition. It is important to realise that tumours may progress through treatment with these cytostatic agents, but at a rate slower than in the absence of treatment. To detect this benefit would require study designs that are used in similar progressive, non-oncological diseases like amyotrophic lateral sclerosis, Alzheimers disease and rheumatoid arthritis,⁸³⁻⁸⁵ which utilise the randomised discontinuation design.⁸⁶

Current phase II trials enrol patients with a specific tumour type. Drugs targeting signal transduction and angiogenesis potentially modulate a common biologic target; therefore future clinical trials with these agents may enrol heterogeneous cancer types sharing the same molecular abnormality or abnormalities.

Conclusion

Phase I and II clinical trials in oncology have led to many new and active agents in current clinical practice, as well as understanding of pharmacological aspects of these agents. However, significant issues remain in the conduct of these studies, and more work needs to be done to address these issues to improve the drug development process. The focus on development of agents that target signal transduction and cancer cell environment poses challenge to those involved in antineoplastic drug development to re-examine the current paradigms of clinical trial design. Deviations from the traditional trial designs are expected.

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