

# Mini-reviews

The first mini-review is a critique of some of the methods used to assess endpoints for drug studies in oncology. The authors review studies using tumour shrinkage and those assessing time to progression. The next paper is a Pubmed-based overview of published reports to establish whether antimuscarinic drugs exert their therapeutic action on detrusor overactivity by reducing the ability of the detrusor to contract. The findings are interesting and somewhat unexpected.

Authors from several centres in Europe review anaesthesiology considerations and requirements for endoscopic extraperitoneal and laparoscopic transperitoneal radical prostatectomy. Finally, a touch of history; we do not have a history section, but occasionally we accept papers dealing with pioneers in urology. Recently we had an Irish pioneer, so it is highly appropriate to include one on a Scottish urological leader, Dr Henry Wade.

## Development of growth inhibitory agents in urological and other malignancies

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In oncology there have been many new putative anticancer drugs based on the improving understanding of oncogenesis and the malignant phenotype. On the basis of their mechanism of action and preclinical data, many of these drugs are expected to inhibit growth. As such, dramatic tumour shrinkage, which has been the classic endpoint for phase II drug studies, might not be a valid or useful measure by which to make decisions as to whether further phase III trials are indicated. Because this is a critical decision point in the overall drug development plan, alternative endpoints and designs need to be considered. More traditional single-arm phase II designs using tumour shrinkage endpoints are reviewed, and the use of randomized phase II designs assessing time to progression discussed. It is postulated that randomized approaches will decrease the current high failure rate for oncological drugs in phase III trials.

### INTRODUCTION

Anticancer drug development, like drug development in other medical disciplines, typically proceeds in a fashion classically divided into phase I, II, III and IV studies. Phase I studies seek to identify toxicity, and the initial dose and schedule at which the drug should undergo further investigation. Phase II studies seek to identify whether the drug has

an antitumour effect and to further explore dose/effect relationships. Phase III studies are the definitive studies used to determine whether the drug provides a true patient benefit, and whether the risk/benefit ratio is clinically relevant. Full regulatory approval of a drug typically occurs only after completing definitive phase III studies. Phase IV studies are post-marketing studies that seek to address specific questions about drug benefit or risk that were not adequately answered in the earlier phase trials. Important in this paradigm is that clinical benefit in oncological phase III studies is typically defined as an improvement in survival or, in the case of adjuvant studies, improvement in time to recurrence. It is also possible to define benefit by delay in symptomatic progression or improvements in quality of life, with perhaps the best example being the improvement in quality of life seen with mitoxantrone in patients with hormone-refractory prostate cancer [1,2]. However, and importantly, phase III studies tend to be large, multi-institutional (and even multinational), long-term and very expensive. Indeed, because of the associated costs, failure of a drug development programme in phase III is considered by the pharmaceutical industry to be a very undesirable event.

Although there are many points in a drug-development plan at which a decision to abort further development can be made, once the drug is in clinical development, the data from

phase II studies is critical in deciding whether to proceed or not [3]. This is perhaps best illustrated by the failure of the metalloproteinase inhibitors in phase III trials that were initiated with minimal preceding phase II data [4–6]. Data suggest that the fraction of phase III trials that are positive is much lower for oncological drugs than for drugs in other medical disciplines [7]. It is thus important to carefully consider the clinical trial designs, including the endpoints, used for phase II studies of novel agents in patients with cancer. The many new agents entering the clinic further emphasize the importance of informative and efficient early-phase clinical trials. To this end it is useful to first consider classical phase II trial design, with a historical perspective that led to the current oncological drug development practices.

### CLASSICAL PHASE II TRIAL DESIGN

Classical oncology drug development has been characterized by the availability of few agents, each of which was quite toxic, and each of which was expected to be cytotoxic. 'Cytotoxic' is generally considered to mean that the agent was expected to kill tumour cells and at least partially eradicate the malignant clone, perhaps more akin to the mechanism of certain antibiotics against micro-organisms. It has also been generally presumed that the 'therapeutic window' (effective vs toxic dose) for these agents is very narrow. As a result, cytotoxic drugs have generally been administered at the maximum tolerated dose and tumour shrinkage (at least for common solid tumours) has been considered a measure of drug effect and efficacy. There has also been a concept that cytotoxic agents are not specifically 'targeted'. However, it may be more accurate to consider these agents to be targeted to DNA replicative and repair mechanism pathways, which are typically dysregulated in cancer cells.

More recently, with greater understanding of the oncological phenotype and of oncogenesis in general, a far larger variety of potential antitumour targets has been identified. These include growth factor-receptor pathways, angiogenesis pathways, apoptosis and growth arrest pathways, senescence pathways, and pathways describing the interaction of the tumour cell with its environment and stroma. Simultaneously, there has been increasing sophistication in the development of

technologies for screening natural products and for chemical synthesis, allowing the production and identification of innumerable new chemical entities that can inhibit these various pathways. The result has been an explosion of putative anticancer compounds that need to be tested.

In addition to the increasing numbers of compounds, it has become recognized that many of the compounds and/or inhibition of many of the potential targets is expected to be growth inhibitory. Even the classical cytotoxic compounds have been suggested to produce cell senescence or [8,9], under certain conditions, to have anti-angiogenic effects [10], both of which would be growth inhibitory more than truly cytotoxic. Thus, tumour shrinkage might not always occur, even for a drug with potent antitumour activity.

Nevertheless, and as stated earlier, the typical endpoint for classical phase II trials in oncology has been tumour shrinkage. This is based not only the presumed effect of cytotoxic agents, but also on the intuitively obvious observation that cancers will continue to grow in the absence of any therapy and therefore shrinkage must represent an antitumour effect. However, it was recognized that evaluating tumour shrinkage, especially in the era before CT scanning, when tumour size was often assessed by direct palpation, was a highly subjective endeavour. In a classical study, Moertel *et al.* [11] showed, by placing rubber spheres of various sizes under a thin mattress, that oncologists could only reliably detect changes in size that were a  $\geq 50\%$  decrease in bi-dimensional measurements. Thus was born the more general rule that shrinkage of  $\geq 50\%$  on bi-dimensional measurements was required before a patient can be deemed to have had a 'response' in a clinical trial.

With the advent of more sophisticated CT scans, certain limitations of always requiring bi-dimensional measurements were recognized and a uni-dimensional system (the RECIST criteria) was instituted [12]. The uni-dimensional criteria for 'response' are simply the geometric equivalent of the decrease in the uni-dimensional diameter of a sphere for which the bi-dimensional orthogonal measurements have decreased by half. Although space limitations preclude a full discussion, several limitations and problems with dichotomizing patients as responders

and nonresponders by these RECIST criteria have been recognized over the years. These include:

- (i) Dichotomization artificially discards inherent information in the continuous changes in tumour size that occur over time, and arbitrarily divides patients into two 'classes' that have little clinical relevance [13]. For example, shrinkage of a group of tumours by 28% has no more or less clinical relevance than shrinkage of 32%, and yet one patient is classified as a responder and the other as stable disease.
- (ii) Partial response is not a surrogate marker as defined by conventional statistical criteria [14]. There are innumerable examples in randomized studies of improvements in response rate that did not lead to improvements in survival, and improvements in survival that were not accompanied by improvements in response rate (e.g. [15–18]).
- (iii) The uni- and bi-dimensional criteria are not completely interchangeable, especially when progression or time to progression is considered, a fact that has been carefully and specifically studied in renal cell cancer [19].
- (iv) Despite numerous attempts at standardization and quantification, the response criteria are still somewhat subjective and interobserver variability remains.

Nevertheless, and despite these limitations, reliable observation of tumour shrinkage in the context of drug treatment still reflects antitumour activity of the administered agent. This is the corollary of the previously stated intuitive observation about cancer; i.e. spontaneous tumour shrinkage or tumour shrinkage through 'divine intervention' is an extremely rare event. In statistical parlance this means that the null hypothesis for a standard defined response rate with an inactive agent is 0% with very tight confidence intervals. Thus was born the typical two-staged design for phase II studies with response rate as an endpoint [20,21]. If there are no responses in an initial small cohort of patients (typically 12–20) it can be stated with a reasonable degree of statistical probability that the response rate is less than a value typically considered to be clinically interesting (e.g. 15% or 20%). However, if there are a certain number of responders, accrual of further patients to the second stage can then proceed. In this case, it is possible to determine whether the true response rate is above the null hypothesis, which is typically set at some nominal value

above 0, that would define an 'uninteresting' drug.

It is important to recognize that these designs will inherently exclude agents or regimens that have little or no cytotoxic activity in a cancer, but will by definition also exclude agents that have antitumour activity by inhibiting growth. Less obvious is that these designs also identify many false-positive results, where the true response rate is above the null hypothesis but much less than that pre-specified as being 'interesting.' In the era of limited agents, this was an inconsequential problem because false-positive results would probably be identified in subsequent studies. However, now that there are many putative agents a second study precludes (or in other words is a lost opportunity) to study perhaps a more interesting agent. This is especially critical given that much, if not most, of the study time comprises initial conception, writing, and approval, with accrual and follow-up representing a much smaller proportion of the entire investment in study time. It thus might be less time-consuming and perhaps even less costly to enrol more patients in one study than to conduct two smaller studies with the same total number of patients.

Given these limitations in classical phase II trial design other approaches should be considered. In this context it is important to consider two separate, but related, aspects of trial design. The first is determining the primary endpoint and the second is the actual design used to assess whether the drug affects the endpoint.

### PHASE II ENDPOINTS FOR GROWTH INHIBITORY AGENTS

As already noted, growth inhibitory drugs are not expected to lead to a sufficient tumour shrinkage that defines an 'objective response' and thus alternative endpoints must be used. It seems natural to presume that the most appropriate endpoint thus should be some measure of tumour progression. Several potential definitions are possible. Most obvious is progression as defined by the classic RECIST or WHO criteria. For a drug that theoretically inhibits metastases the development of new lesions could potentially be considered as an endpoint, but clinical situations in which significant growth in existing lesions is clinically deleterious would

have to be accounted for, even though the trial endpoint has not been met. Any of these criteria are quite arbitrary and it would be possible to construct a trial-specific definition of progression that is clinically reasonable.

One endpoint in urological malignancies that is often used for clinical management is the change in PSA level for patients with prostate cancer. This has been driven by the limitations in bone scintigraphy for assessing disease activity, and the frequent lack of measurable visceral or nodal disease in these patients. Certainly, a persistent increase in PSA level is generally considered to be clinical evidence of progressive disease in these patients. Much has been written about PSA as a biomarker and its use as a clinical trial endpoint with many, if not most, emphasizing that it is not a surrogate marker as defined by standard statistical criteria [22–25]. As radiological markers more typically used in phase II clinical trials are not surrogate markers either, this in and of itself should not preclude its use.

However, there are two very specific issues that need to be considered when using PSA level as a marker of progression in clinical trials. The first is that some care must be taken to consider whether the agent under investigation could affect PSA secretion without affecting tumour growth. The second is to recognize that PSA measurements can be somewhat variable from one laboratory to another, and that any two sequential values might not reflect the overall pace of disease. This is especially critical if there is an attempt to measure an effect on PSA kinetics. For example, in a placebo-controlled trial of rosiglitazone in patients with early castration-resistant disease, 40% of patients in the placebo group increased their PSA doubling time by at least 150% from a pretreatment value estimated by historical values obtained before study enrolment [26].

### PHASE II CLINICAL TRIAL DESIGNS FOR GROWTH INHIBITORY AGENTS

Quite distinct from the choice of endpoint, but obviously related, is the trial design used to assess a growth-inhibitory effect in a phase II trial. Unlike the situation with cytotoxic drugs, where tumour shrinkage sufficient for a standard radiological response is extremely

rare in the absence of treatment (or equivalently with an inactive drug), time to progression is highly variable. This might be especially true of urological malignancies such as prostate and renal cancer, in which the natural history can be quite long.

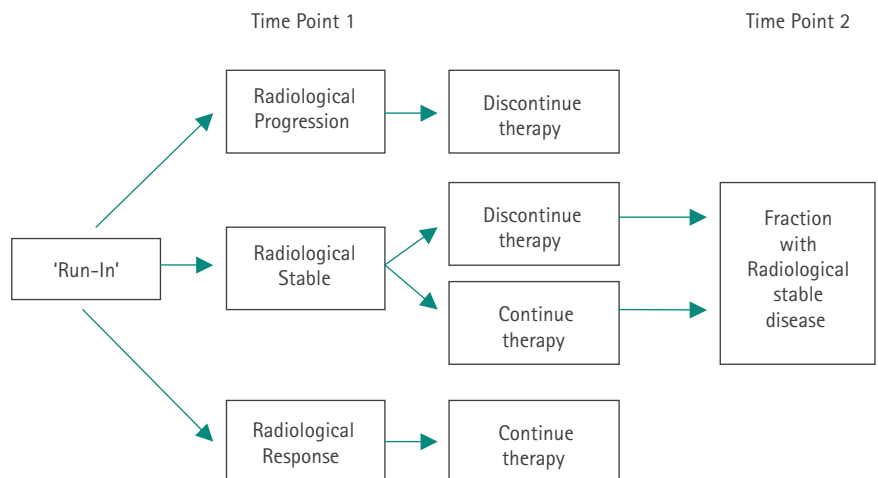
Increasingly sophisticated prognostic models decrease this variability somewhat, but do not completely abrogate it [27–30]. Uncontrolled single-arm studies with some type of 'time-to-progression' as an endpoint, which by definition needs to be compared to expected outcome from a historical control, will thus be difficult or almost impossible to interpret. In other words, if the observed time to progression is longer than expected, it will not be possible to determine whether this was due to enrolment of a group with a better prognosis or due to the study agent. Conversely, if the time to progression is no different from that expected, it is not known whether the enrolled group might have had a somewhat worse prognosis, and whose outcome was improved by the administered agent.

One way in which to address this is to assess the pace of disease or growth rate before and after administration of the agent. However, using historical available clinical data before entry into a trial is problematic. To estimate appropriate growth rates before therapy, the measurements must be taken in the same way and at the same interval as will be done after therapy. Furthermore, several measurements will probably be needed with no treatment, to obtain a good estimate of the tumour growth rate. In effect, this requires that patients be enrolled in a trial and observed or treated with placebo for several months before receiving the investigational agent. Even then, some statistical assumptions, e.g. correlation of the growth rate before and after treatment, might not be met [31]. For example, the previously noted increase in PSA doubling time in a placebo-treated cohort is probably due to an insufficient observation time before enrolment and the resulting 'regression to the mean' of extreme values. In addition, if patients are enrolled and observed before treatment, analysis of patients who are not able to receive the investigational therapy due to rapidly progressive disease is complicated. For example, excluding such patients from the analysis means that the worst group of patients is eliminated, which from a statistical standpoint is a type of 'informative missingness'. A more acceptable trial design to assess time to progression is with the use of a

concurrent control. The simplest and most straightforward control would be a placebo. The use of placebos in patients with advanced cancer is often criticised, but in clinical scenarios where there are no standard effective therapies and the experimental therapy has known or expected toxicities, it might be justified. The challenge with this classical design is that many patients will be required, of whom the proportion benefiting from the agent might be small. Some have argued that if a large trial is conducted it might be better to simply design a phase II/III trial that could be stopped early if pre-specified phase II endpoints are not met [32,33]. This might be feasible because the only difference between a placebo-controlled randomized phase II and phase III trial is the endpoint, with the phase II endpoint generally occurring earlier (e.g. time to progression vs survival). Nevertheless, such a design needs to be balanced against the increased monitoring, expense, and statistical rigour required for definitive confirmatory trials, as opposed to the more exploratory 'learning' trials conducted in phase II [34].

Randomized phase II trials have been criticised as being under-powered phase III trials that are often misinterpreted. Once again the more critical difference between a phase II and III trial is the endpoint and not the design. For phase II studies the endpoint is one that reflects an antitumour effect, whereas in a phase III study, the endpoint reflects true benefit to the patient. It is also reasonable to power randomized phase II trials at very different levels than would be acceptable in a phase III trial. For example, assessing whether an agent can increase the time to progression from 4 to 6 months (hazard ratio of 1.5) with 80% power and a one-sided  $\alpha$  of 0.1 would require only  $\approx 65$  patients per group. It is recognized that 10% of such trials might be 'false-positives' and that a one-sided test is inappropriate for a definitive phase III study, but those odds might be sufficiently low to justify the expense of conducting a subsequent definitive trial. This false-positive rate is also lower than the false-positive rate discussed earlier for single-arm phase II trials with tumour shrinkage as the endpoint. Likewise, it is recognized that there is a 20% chance of missing an active drug or one that has a more modest clinical effect than the rather aggressive hypothesized improvement. In an age of limited agents this would have been a

FIG. 1. A schematic diagram of the randomized discontinuation trial.



critical error, but in the modern era with many agents and many potential targets, it might be more fruitful to evaluate a different therapeutic approach.

Another randomized design that could be used to evaluate a new growth inhibitory agent is to give a standard treatment to both groups, and add the investigational agent in one. Although not unreasonable, this design effectively changes the underlying hypothesis from one in which the new agent is independently active to one that it potentiates standard therapy. It is certainly theoretically feasible that an agent which has no independent activity could potentiate the activity of a cytotoxic agent. Conducting such 'add-on' trials also requires detailed knowledge about the interactions between the investigational and the standard agent, including potential interdependent effects on pharmacokinetics or toxicity.

A final randomized approach to consider is the randomized discontinuation trial (Fig. 1) [35]. With this design all patients receive the drug initially, and those who progress by arbitrary criteria before a randomization time some weeks or months after enrolment are discontinued. Those patients who have clear evidence of an antitumour effect using the typical radiological criteria by the randomization point continue with open-label therapy. Those patients who maintain stable disease at the randomization point are then randomized to continue or discontinue the agent in a double-blind manner. The primary endpoint for this design is the fraction of patients in each of the randomized

groups who maintain stable disease for a specified period after randomization. The advantages of this design include that all patients receive the investigational agent initially, thus precluding the 'placebo problem', fewer patients are exposed to placebo, and in certain situations fewer patients overall are enrolled than in an initial placebo vs drug trial [36]. Perhaps the most powerful aspect of this trial design is that the agent 'selects' the population most likely to benefit, as opposed to the investigator selecting the most appropriate group, using incomplete clinical and biological knowledge. It has been shown for example that this trial design is especially powerful in detecting antitumour activity if the proportion of patients benefiting is low ( $\leq 30\%$ ) [37]. With increasing recognition and description of solid tumour subtypes within a disease that was previously considered to be one cancer (see e.g. [38]), each with potentially different therapy, this latter characteristic might become particularly useful. In urological malignancies, this trial design was used successfully to show that the putative anti-angiogenic agent carboxyaminoimidazole has no activity in metastatic renal cancer, whereas the agent sorafenib does [39,40].

## CONCLUSIONS

More putative anticancer agents against an increasing number of putative targets have been or are in the process of being developed. Many of these agents are expected to be growth inhibitory. As a result, the classical single-arm uncontrolled phase II trial design

with radiological shrinkage as the primary endpoint should be reconsidered. For a growth inhibitory drug some measure of disease progression is a reasonable endpoint. However, in this case a control group is required to be able to interpret whether any observed value can be attributed to a drug effect. More specifically, because of the highly variable natural history of many cancers, especially those such as prostate or renal cancer, which is not completely accounted for by current prognostic models, a concurrent control group is generally required. The trial designs that accomplish this include drug vs placebo, standard therapy with or without new drug, or the randomized discontinuation design. Although each of these designs has its advantages and disadvantages, the use of a concurrent control group and a measure of disease progression as the primary endpoint is a common theme that will probably have to be incorporated in many future phase II trials. Hopefully this will increase the fraction of phase III trials that are positive, which in turn will decrease the overall financial and time cost of developing new drugs for patients with cancer.

#### CONFLICT OF INTEREST

The author is consultant to Bayer, Onyx, GlaxoSmithKline, Novartis, Genentech, AstraZeneca, Abbott, Amgen, Takeda. Grant/research support: Bayer, Onyx, Bristol Myers Squibb, Novartis, Genentech, Wyeth, AstraZeneca, Exelixis, Medarex, Medimmune, Agenix, Solvay, Pfizer, Innohep, Eli Lilly.

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