Early phase cancer clinical trials: design, ethics and future directions

The main role of early phase clinical trials in cancer is to determine the dose to take forward for future clinical study. However, study design is changing in order to account for the change in focus of drug development toward molecularly targeted agents.

Cancer drug development has, over the past 60 years, become a defined process. Initially preclinical data are generated in the laboratory using both in vitro and in vivo assays before human studies, first to understand whether a compound has promising anticancer activity, second to assess how a drug is absorbed, distributed, metabolized and excreted in mammals, and last to start to investigate how best patients might be selected for the drug. The first step in taking drugs into patients occurs in phase 1 trials for which the main aim is usually to understand the dose(s) of a drug (or drug combination) to take forward for further study. This involves a process of dose escalation typically within cohorts of patients until toxicity is defined to be too great. In general, a single agent or drug combination is then taken through further development phases, initially assessed in phase 2 trials to understand drug toxicity, bioactivity and objective cancer response rates more fully before testing efficacy *vs* standard treatment in a randomized controlled phase 3 trial.

This review discusses the considerations that should be given toward the design of early phase cancer trials, their ethical issues and current challenges, and the changing role of early phase trials in drug development.

Early phase trial design

The design of dose escalation studies is guided by three key principles: maintaining patient safety, avoiding exposure to subtherapeutic dosing for as many patients as possible and ensuring that the recruitment to a study can be as rapid and efficient as possible.

Established methodology for determining the starting dose of a drug from preclinical toxicology studies recommends that the drug be tested in at least two mammalian species with dose escalation designs to determine the lethal dose in 10% of animals (LD10). Most commonly the starting dose used for a first in man phase 1 trial is 1/10th the LD10 equivalent. Data from animal studies on the pharmacokinetics of a drug can also inform study design in terms of helping to determine dosing schedules. An understanding of which organs are involved in excretion of the drug and whether a particular enzyme system is important in its metabolism, such as cytochrome P450, will help in determining the inclusion and exclusion criteria (for example whether patients with abnormal liver or renal function are excluded or certain concomitant medications are not allowed). Last the relationship between animal pharmacokinetic measurements (e.g. plasma drug level) and target effect in both normal and tumour tissue may help inform expected therapeutic dose levels in humans (Goodwin et al, 2012).

In general, the patient population recruited to phase 1 trials testing anti-cancer drugs that are ‘first in man’ is composed of patients with cancers for which there is no effective standard treatment left available. Other considerations also apply with regards to the criteria for study entry including performance status (i.e. ‘general wellbeing’ of the patient), organ function, comorbidities and concomitant medications. A more recent consideration for molecularly targeted agents that have been designed to target a particular tumour subtype is to select patients on the basis of a predefined biomarker, for example HER2 positive breast cancer (Yap et al, 2010).

The principle of defining the highest tolerable dose of cytotoxic drugs in phase 1 trials was established early on from experiments that showed there was a direct relationship between dose and cell kill (Skipper et al, 1964). Most phase 1 trials are classical dose escalation studies in which doses of the drug are escalated in cohorts of patients until a maximum tolerated dose is reached. The maximum tolerated dose is typically defined as the dose level at which one third of patients in the cohort suffer a dose-limiting toxicity, most usually within the first cycle of treatment. The trial protocol will predetermine what toxic effects represent a dose-limiting toxicity (see

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Table 1 for some common examples). In actual fact the dose that is taken forward into phase 2 is usually a dose level below that of the maximum tolerated dose as significant toxic effects would be expected at this dose level and in too many cases may be severe (Anonymous, 1985).

The '3+3' dose escalation design

The classical phase 1 trial schema is the '3+3' design (see *Figure 1* for study schema) in which, initially, a cohort of three patients is enrolled at the starting dose level. Should there be no dose-limiting toxicity within that cohort the dose is then escalated to the next dose level. However, if a study participant does experience a dose-limiting toxicity a further three patients are recruited at that dose level. Should a further dose-limiting toxicity be experienced in the expanded cohort the maximum tolerated dose will have been reached (one third of patients will have suffered a dose-limiting toxicity). If on the other hand two out of the initial three patients recruited to that dose level suffer a dose-limiting toxicity the dose level below is normally expanded. Historically, the spacing between each dose level follows a modified Fibonacci series so that the relative increase between each dose level remains constant (each dose being approximately two thirds larger than its predecessor).

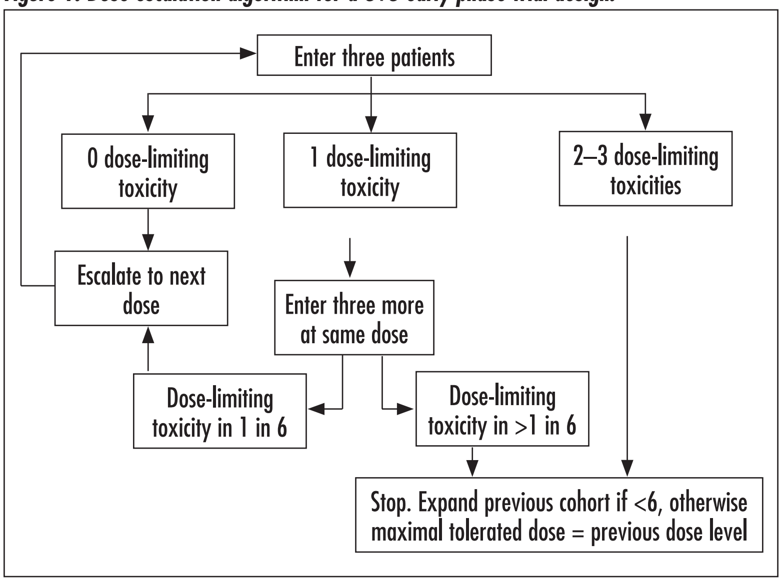
Criticisms of the '3+3' schema include the length of time that recruitment can take, the fact that many patients are treated at doses with minimal chance of efficacy and that too few patients are treated at dose levels around the maximum tolerated dose (Eisenhauer et al, 2000). Modified trial designs have attempted to address this and are becoming more popular but discussion of these is not within the scope of this review. For a more detailed discussion of phase 1 trial design, see Ivy et al (2010).

Table 1. Examples of defined dose-limiting toxicities in a study of chemotherapy in combination with a MEK inhibitor

Dose-limiting toxicities are defined as any of the following, where attributable to the study drug:
Grade 4 neutropenia lasting >7 days
Grade 3/4 neutropenia associated with sepsis or with fever >38.5°C
Grade 4 thrombocytopenia
Symptomatic visual disturbance which does not recover within 5 days
Grade ≥3 rash which persists for 5 days or more despite optimal treatment
On electrocardiograph, QTc >530 msec (Bazett's)
Grade ≥3 other non-haematological toxicities, except for alopecia, and nausea or vomiting unless patients are taking optimal prophylaxis and/or supportive measures
Delay of >2 weeks in start of cycle 2 of treatment because of toxicities

From Coupe et al (2015)

Figure 1. Dose escalation algorithm for a 3+3 early phase trial design.



Pharmacokinetic *vs* pharmacodynamic studies

Traditionally, other than establishing the maximum tolerated dose for a novel agent a focus has been put on measuring the pharmacokinetic profile of drugs, i.e. 'what the body does to the drug'. To understand the absorption, distribution, metabolism and excretion of the drug most commonly a series of timed blood samples are taken which allow the measurement of the plasma concentration of the drug and its metabolites. Other samples such as urine (especially if drug undergoes renal excretion), CSF or normal and tumour tissue may also be examined. The drug concentration will then typically be plotted against time on a logarithmic scale. This allows calculation of the area under the curve – a parameter that reflects total body exposure and will be determined by both the dose and clearance of the drug. Other key parameters routinely measured are the total plasma clearance, terminal half life and volume of distribution (*Table 2*). The C_{max} is a measurement of maximal plasma concentration of the drug and often correlates well with drug toxicity (Anonymous, 1985).

However, two considerations have led to increasing interest in understanding the pharmacodynamic effects of a drug in early phase trials or 'what the drug does to the body/tumour'. First, the standard designs for these studies were developed in an era when virtually all cancer drugs being tested in the clinic were cytotoxic agents. Now design is evolving to accommodate molecularly targeted drugs that may not have very toxic effects at therapeutic doses or cause significant tumour regression and may only have benefit in highly defined tumour subpopulations (Yap et al, 2010). Second, the vast efficiencies in preclinical cancer drug development gained by our understanding of cancer biology and improved chemistry has led to a much greater number of compounds being taken forward into the clinic and hence a need for early phase trials to screen out less promising drugs at an early stage in their development.

The fallout from Northwick Park

Public confidence in the design and management of early phase trials was shaken by the widely reported 'Northwick Park disaster'. This was a phase 1 study in which all six healthy volunteers entered onto the study suffered a cytokine storm in response to treatment with an anti-CD28 monoclonal antibody, a proposed therapy for rheumatoid arthritis, leukaemia and multiple sclerosis. Although no deaths occurred, all six patients developed multiorgan failure, two required mechanical ventilation and the worst affected had several fingers and toes amputated (Suntharalingam et al, 2006). The incident led to four reports from the Medicines and Healthcare Products Regulatory Agency and an investigation by Professor Gordon Duff. The Duff report made 22 recommendations calling for independent expert advice to be sought before high risk studies go ahead, the pooling of information from unpublished or abandoned studies and that for first in man studies an investigational drug should be given to one participant at a time and slowly by infusion, rather than as a bolus injection (Duff, 2006).

Current evidence suggests that in fact early phase cancer trials are remarkably safe. Patient mortality is reported to be approximately 0.5% and the figure for deaths directly or at least probably related to the investigational medicinal product is even lower at 0.21% (Decoster et al, 1990; Roberts et al, 2004; Horstmann et al, 2005). Trials involving cytotoxic chemotherapy typically had a higher mortality rate compared with drugs targeting signal transduction pathways and immunomodulatory agents. Morbidity, defined as grade 3 or 4 toxicity, occurs in an estimated 10–14% of patients, again with higher figures in 'classic' monotherapy chemotherapeutic trials (Roberts et al, 2004; Horstmann et al, 2005).

Although phase 1 trials are generally safe, expectation with regards to patient benefit has to be tempered. Based on a meta-analysis of outcomes from over 400 phase 1 trials between 1991 and 2002 the canonical overall response rate (both partial and complete response rate) for patients in phase 1 trials is quoted at between 5 and 10%. Interestingly, only 22% of trials conducted over this period evaluated single agent cytotoxic therapies (referred to as classic phase 1 trials), and indeed the response rate in these trials was dismal, averaging less that 5%. Most studies involved the use of more than one cytotoxic drug, frequently in combination with drugs targeting receptor or transducer pathways or the immune system. When outcomes from these studies were included, the overall response rate was considerably higher, at over 10%, and when the definition was broadened to include those patients achieving stable disease, the figure approached 50% (Horstmann et al, 2005). Phase 1 trials involving newer molecularly targeted treatments occasionally demonstrate dramatic results. For example, early trials of vemurafenib in patients with BRAF mutant melanoma and imatinib in chronic myeloid leukemia resulted in response rates of 70% and 98% respectively (Druker et al, 2001; Flaherty et al, 2010). The changing landscape, in which cancer biology is far better understood and where treatments are 'designed' rather than 'screened for', suggests the traditionally dire view with regard to the chances of patient benefit from entry into

Table 2. Definitions of common abbreviations

Definition (abbreviation)	Meaning
Pharmacokinetics (PK)	The effect of the body on the drug (absorption, distribution, metabolism, elimination)
Pharmacodynamics (PD)	The effect of the drug on the body (both desired and undesired)
Maximum tolerated dose (MTD)	The highest dose of a drug or treatment with acceptable side effects
Dose-limiting toxicity (DLT)	Side effects which are severe enough to limit further escalation of the dose of a drug
Recommended phase 2 dose (RP2D)	The dose recommended for further testing in phase 2 trials
Lethal dose 10% (LD10)	The dose at which 10% of animal test subjects die
Area under the curve (AUC)	A representation of the total drug exposure integrated over time
Terminal (or elimination) half-life (t1/2)	The time taken for the plasma concentration of a drug to reduce by half
Clearance (CL)	The volume of plasma cleared of drug per unit time
Volume of distribution (Vd)	The theoretical volume of plasma into which the total amount of drug administered would have to be diluted to produce the measured plasma concentration. It is a measure of the distribution of drug between plasma and tissue
Maximal plasma concentration (C_{max})	The highest concentration of the drug measured in the plasma
Therapeutic index (TI)	A ratio of the amount of drug that causes a level of toxicity to the amount of drug that produces a therapeutic effect
Entry criteria	The inclusion and exclusion criteria for enrolling participants into clinical trials
Eastern Cooperative Oncology Group Performance Status (ECOG PS)	A widely used scale for assessing the impact of disease on the general health and daily abilities of a patient

early phase trials needs reassessing. Additionally, patients on phase 1 trials may receive benefit in terms of improvements in supportive care, the sense of altruism and psychological reassurance associated with regular medical contact (Hutchison, 1998; Moore, 2001).

Should novel agents be available to all?

The long process of drug development has resulted in a growing clamour for terminally ill patients to have access to untested experimental therapies outside of the clinical trial setting. In the UK this led to the proposed and subsequently defeated 'Saatchi bill' which sought to 'clarify' the legal framework by which novel treatments could be given to patients outside of clinical trials (Raftery and Newdick, 2014; Rawlins, 2014). Similarly, in the USA, right-to-try laws have been enacted in five states allowing patients to have treatments without oversight of the Food and Drug Administration provided they have been tested in phase 1 trials (Okie, 2006; Nature Medicine, 2014). As many in the clinical research community have pointed out, allowing patients to take untested drugs may well harm trial recruitment and the feasibility of determining their safety and clinical benefit which may ultimately not be in the best interests of the majority of patients. Equally, it is important to understand the very real frustrations of patients with terminal illness who do not meet the tight eligibility criteria for clinical trials or live far from research centres.

Future directions

In general, dose escalation methods for phase 1 trials have used toxicity as an end point for determining the maximum tolerated dose, under a historical assumption that toxicity parallels efficacy. While this model is applicable to cytotoxic drugs for which cancer cell kill is typically directly related to dose, different approaches are needed for newer molecularly targeted therapies. Application of traditional trial designs for these therapies may result in determination of an maximum tolerated dose and hence toxicity much higher than the therapeutically effective dose (Fox et al, 2002; Kummar et al, 2006). The use of pharmacodynamic end points allows for rapid dose escalation, accurate determination of an effective dose and avoids unnecessary exposure of patients to dose levels above those which demonstrate an appropriate level of bioactivity. However, this requires a validated assay to demonstrate target inhibition, knowledge of what constitutes an effective level of target inhibition and ready access to tumour samples. Consequently, thorough preclinical work is required to ascertain these parameters before commencing a phase 1 trial. Use of pharmacodynamically determined endpoints also requires ready access to patient tumour samples, which in itself presents safety, logistical and potentially ethical barriers. Surrogates of tumour tissues are an alternative method to determining biologically effective doses without the need for invasive tumour biopsies. For example, peripheral blood mononuclear cells can be sampled for this process. However, such an approach is only effective if a precise relationship between target inhibition on peripheral blood mononuclear cells and tumour can be validated pre-clinically in animal and in vitro models (Kummar et al, 2006). Likewise, functional imaging can serve as non-invasive surrogate of biological activity. An example is the use of dynamic contrast-enhanced magnetic resonance imaging as a biomarker for the assessment of drug effect on angiogenesis (Liu et al, 2005).

Traditional phase 1 trials determine the recommended phase 2 dose based upon a definition of dose-limiting toxicities occurring within the first treatment cycle. Newer molecularly targeted therapies are frequently administered indefinitely until disease progression or unacceptable toxicity. This is in contrast to cytotoxic drugs, which are often given for a fixed number of cycles. The prolonged administration of molecularly targeted treatments frequently results in toxicities meeting dose-limiting toxicity definitions beyond cycle 1. Postel-Vinay et al (2011) reviewed toxicity data from 36 phase 1 trials evaluating targeted therapies. Here, 57% of patients suffered grade 3 or 4 toxicities after cycle 1 and half of all patients experienced their worst toxicity beyond this same time point. Evidence of such delayed toxicity gives merit to the consideration of 'chronic dose-limiting toxicities' in the determination of the final recommended phase 2 dose, although this remains to be adopted across all phase 1 trial designs.

Conclusions

Traditional dose escalation trials remain a vital process for cancer drug development. However, more information is now being sought from these studies, in particular with regards to the drug effect on tumour tissue so that unpromising compounds can be identified and discarded at an early stage in their development, and to get a grasp of how best to select patients for future trials. These are exciting times for cancer drug development as new technologies, such as whole cancer genome and transcriptome sequencing of tumours, will allow us to understand drug resistance and potential drug combinations early on

KEY POINTS

- The main role of early phase trials is to find the appropriate dose level to take forward for further study.
- The design of studies is changing as novel molecularly targeted drugs replace cytotoxic agents.
- How best to use new technologies such as genomics and novel cancer imaging is a major challenge but a great opportunity.
- The Northwick Park incident has altered public perception of and confidence in drug development.
- The potential impact of recent legislative proposals for wider access to experimental drugs on clinical research needs to be considered.

in the development pathway. However, significant challenges remain, including an ever-increasing regulatory burden, public perception following Northwick Park and a growing clamour for unproven drugs to be used outside clinical trials for terminally ill patients. **BJHM**

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