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New regulatory framework for cancer drug development

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Recent changes to non-clinical cancer guidelines offer a golden opportunity to expedite the translation of new anticancer drugs into the clinic. In this review we look at how these guidelines can be implemented and how they can be integrated with non-clinical and clinical study design to produce robust and safe clinical trials.

Introduction

Clinical trials are undertaken to enable data regarding the safety and efficacy of new products to be collected. These trials can be conducted using healthy volunteers or patients, depending on the type of product and its stage of development. Information on non-clinical safety will have been obtained before the clinical trial programme commences. Clinical trials begin with small studies in a controlled population of healthy volunteers or patients and, as data are gathered, expand to large-scale studies in patients. These large-scale studies will often investigate the new product and the currently used treatment to see how the two compare. As information is obtained, larger numbers of patients are exposed to the new product and safety data can be collected demonstrating the safety of the product in the intended patient population.

Harmonisation of regulatory requirements was pioneered by the European Union (EU) in the 1980s, as it moved towards the development of a single market for pharmaceuticals. The success achieved in the EU demonstrated that harmonisation was feasible, and at the same time there were bilateral discussions between the EU, Japan and the USA on possibilities for further harmonisation.

The birth of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) took place at a meeting in April 1990, hosted by the European Federation of Pharmaceutical Industries and Associations in Brussels. Representatives of the regulatory agencies and industry associations of the EU, Japan and the USA met, primarily, to plan an International Conference, but the meeting also discussed the wider implications and the ICH terms of reference. At the first ICH Steering Committee meeting the Terms of Reference were agreed and it was decided that the topics selected for harmonisation would be divided into safety, quality and efficacy to reflect the three criteria, which are the basis for approving and authorising new medicinal products.

Recent changes in guidelines affecting oncology products

In the UK the Medicines and Healthcare Products Regulatory Agency (MHRA) Clinical Trials Unit has the role of assessing applications from sponsors to conduct clinical trials with medicinal products. A significant proportion of clinical trials conducted in the UK relate to oncology indications (i.e. approximately 30% of all open UK trials[†]). There are a number of regulatory guidelines, international (ICH) and EU-specific, available, many of which deal directly or indirectly with oncology products [1–6].

The introduction to the anticancer guideline ICH S9 [3] states that 'the guidance provides recommendations for non-clinical evaluations to support the development of anticancer pharmaceuticals in clinical trials for the treatment of patients with advanced disease and limited therapeutic options'. This guideline aims to help accelerate the development of anticancer drugs while protecting patients from unnecessary adverse effects (Table 1).

In the development of anticancer drugs, the clinical trials often involve cancer patients whose disease condition is progressive and usually fatal. The dose levels in these studies are often close to or at

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[†] Based on a search of clinicaltrials.gov for all open trials versus open cancer trials in the UK on 7 December 2011.

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TABLE 1

Major guidelines relevant to the development of agents for oncology indications

ICH topic	Guideline	Ref
S9	Non-clinical evaluation for anticancer pharmaceuticals	[3]
M3 (R2)	Non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals	[6]
S6 (R1)	Pre-clinical safety evaluation of biotechnology-derived pharmaceuticals S6	[1]
N/A	Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products	[4]
N/A	Guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products	[2]
N/A	Guideline on the non-clinical development of fixed combinations of medicinal products	[5]

Abbreviation: N/A, not applicable.

the adverse effect dose levels. Obviously, therefore, the type, timing and flexibility called for in the design of non-clinical studies of anticancer pharmaceuticals should differ from these elements in animal studies for most other therapeutic indications. The ICH S9 [3] guideline applies to small-molecule and biotechnology-derived pharmaceuticals (biopharmaceuticals), regardless of the route of administration, and refers to the corresponding ICH guidelines M3 (R2) [6] and S6 (R1) [1].

The ICH S9 guideline describes the minimal considerations for initial clinical trials in patients with advanced cancer, whose disease is refractory or resistant to available therapy, or where current therapy is not considered to be providing benefit. The non-clinical data to support Phase I clinical trials, and the subsequent clinical data from those trials, would normally be sufficient for moving to Phase II and then into second-or first-line therapy in patients with advanced cancer. The guideline then describes further non-clinical data to be collected during continued clinical development in patients with advanced cancer. The guideline makes it clear that when an anticancer pharmaceutical is investigated in cancer patient populations with long expected survival (e.g. those administered pharmaceuticals on a chronic basis to reduce the risk of recurrence of cancer) the recommendations for, and timing of, additional non-clinical studies will be more substantial. The guideline does not apply to pharmaceuticals intended for cancer prevention, treatment of symptoms or side effects of chemotherapeutics, studies in healthy volunteers, vaccines, or cellular or gene therapy.

The primary objective of Phase I clinical trials in patients with advanced cancer is usually to assess the safety of the product and can include dosing to a maximum tolerated dose (MTD) and dose-limiting toxicity. Accordingly, non-clinical toxicology studies designed to determine a no observed adverse effect level or no effect level are not considered essential to support clinical use of an anticancer pharmaceutical and a similar MTD approach to that used in Phase I clinical trials in oncology is often adopted.

Toxicity studies

The toxicity of a product can, of course, be greatly influenced by its schedule of administration; an approximation of the clinical schedule should therefore be evaluated in the non-clinical toxicology studies. The non-clinical dosing schedule need not necessarily be identical to the intended clinical schedule and it is common to see a more frequent dosing schedule used in animals. Such an approach can lead to greater flexibility in early phase clinical trials, which can be the key to successful translation.

An assessment of the potential to recover from toxicity should normally be provided to understand whether serious adverse effects are reversible or irreversible. There is, however, an argument that such data need not be generated for the initial studies in humans, especially if there are sufficient data on the observed effect to make an informed assessment of the likelihood of reversibility. A study that includes a terminal non-dosing period is only called for if there is a severe toxicity at approximate clinical exposure and recovery cannot be predicted by the scientific assessment.

For small molecules, the general toxicology testing recommended by ICH S9 [3] usually includes rodents and non-rodents. At first sight, this appears to be different from the previous EU-specific guidance [7]. The earlier EU guidance stated that, 'a repeat-dose toxicity study of limited duration (two to four weeks or one to two cycles) in two rodent species should be performed prior to Phase I studies'. However, ICH S9 [3] also includes the statement: 'In certain circumstances, determined case-by-case, alternative approaches can be appropriate ... a repeat-dose toxicity study in one rodent species might be considered sufficient, provided the rodent is a relevant species'. In fact the earlier EU guidance also stated that, for compounds with a novel mechanism of action, studies needed to be performed in a rodent and a non-rodent species.

Other safety studies

Embryofoetal toxicity studies (to communicate the potential risk to the developing embryo or foetus in patients who are or might become pregnant) are not considered essential to support clinical trials in advanced cancer. Many of the patients will have already received prior therapies that will have compromised their fertility. However, the MHRA does expect that Phase I protocols consider appropriate contraception advice for a patient who might be fertile and sexually active. A study of fertility is also not warranted to support clinical trials intended for the treatment of patients with advanced cancer. Information available from general toxicology studies on the pharmaceutical's effect on reproductive organs should be used as the basis of the assessment fertility impairment.

Genotoxicity studies are also not considered essential to support early clinical trials for therapeutics intended to treat patients with advanced cancer, and for most anticancer products the general toxicology studies should be sufficient to evaluate potential immunotoxic potential. For immunomodulatory compounds, additional endpoints (such as immunophenotyping by flow cytometry) can be included in the non-clinical studies.

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An initial assessment of phototoxic potential should be conducted prior to Phase I, based on photochemical properties of the drug and information on other members in the class. If assessment of these data indicates a potential risk, appropriate protective measures should be taken during outpatient trials. If the photosafety risk cannot be evaluated adequately, based on available non-clinical data or clinical experience, a photosafety assessment consistent with the principles described in ICH M3 (R2) [6] should be provided before marketing. It is also worth noting that an ICH guideline on photosafety evaluation (ICH S10) is currently in development with a draft for public consultation expected in June 2012.

Implications for non-clinical cancer drug development

Taken altogether, the guideline changes discussed above enable a major shift in the studies required to support translation of cancer therapeutics to the clinic. In this section we will discuss the implication of these changes in terms of regulatory requirements and the requirements for a biologically informed translation to facilitate further development.

The ICH S9 guideline [3] requires minimal efficacy work before the first-in-human (FIH) clinical trial, merely requesting studies to provide non-clinical proof of principle, guide schedules and dose-escalation schemes. Pharmacokinetic (PK) work (i.e. ADME) can be limited to an evaluation of basic parameters, C_{max} and AUC, and little else. Although this low requirement for characterisation before FIH can accelerate translation of a new drug to the clinic, there is a danger that this could take place before adequate understanding of the pharmacology of the drug is attained to build a clinical protocol on a sound scientific basis. This has the potential to expose patients to risk without clear benefit unless extremely overt efficacy is observed. How can non-clinical work be optimised to enable smooth translation to the clinic?

Model characterisation

In general, toxicology studies on small molecules intended for oncology treatment have generally been performed using rat and dog models, whereas the majority of anti-tumour efficacy studies have used mice bearing human xenografts. The EU risk mitigation guideline discusses in detail species choice based on biological relevance and it is important that this is considered and species choice justified early in non-clinical development – especially with biological agents [4].

When translating highly selective molecularly targeted agents into humans an understanding of the relevance of efficacy models and on-target pharmacology could be just as important as the relevance of safety models. The non-specific mechanism of action of most cytotoxic drugs and the high sequence conservation of many kinase targets have enabled considerable success in the absence of such understanding [8]. However, as agents become more selective, on-target pharmacology and toxicology could become part of a continuum of desired and undesired effects. For example, there could be little toxicity at all, toxicity purely as a result of target over inhibition/activation, the target might only be expressed on tumours or the drug could be a drug precursor only activated to the compound within the tumour. At present not enough consideration goes into comparing target pharmacology between non-clinical efficacy species and safety species, which can make extrapolating safety and efficacy findings to the clinic challenging. An understanding of target similarity between species informs work with xenografts, where the interaction between the tumour and stroma is xenological, and syngeneic models, where the entire model system is in a non-human species [9,10]. The conduct of studies using different species for evaluation of efficacy and safety could also be unhelpful because it does not provide a direct estimate of therapeutic index in a single species.

A greater understanding of the pharmacology of potential models could also inform not only choice of model but a choice not to perform toxicology studies at all. In certain cases a response (be it toxicological or pharmacological) might be so species- and context-specific that a toxicology study might yield results that are at best uninformative and at worst misleading. In such cases a reliance of efficacy work and a review of the available relevant published information might be the best available option.

Efficacy studies in vitro

In vitro work in cancer has traditionally focused on tumour cell-line growth inhibition or lethality (GI_{50} or LC_{50}) prior to work in tumour xenograft mice; an approach supported by screens such as the NCI60. However, for targeted therapeutics this information alone does not give an adequate basis for rational translation. Even at this early stage of development a good understanding of the relationship between drug exposure and biological effects on the target is required – for which biomarkers are clearly needed [11]. These biomarkers should not just look at the ability of the drug to hit its target but also at its ability to have effects on downstream signalling – ruling out rapid proximal resistance by modulation of downstream signalling through feedback loops. The term biomarker is used here in a general sense and covers assays on tumour tissues *ex vivo*, surrogates of tumour effects in body fluids and imaging of effects on a tumour *in vivo*. The definition of the various kinds of biomarkers is discussed on the CRUK website.[‡] The presence of such markers enables an easy characterisation not just on the concentration:effect relationship but also of the duration of that effect once the therapeutic is removed. Although this information is useful for optimising growth-inhibition assays, it also facilitates transition to *in vivo* models based on the concentrations required at the tumour and the duration for which those concentrations are required.

Efficacy studies in vivo

One of the key stages in the non-clinical development of new therapeutics is the switch from *in vitro* to *in vivo* models; however, this is often performed too late in the development of a drug and without adequate consideration of the future translation to the clinic. To ensure smooth translation to the clinic, the end stages of non-clinical lead optimisation should be performed *in vivo* to enable selection of a clinical candidate compound that is safe, efficacious and can reach the target in a schedule that is achievable clinically. If the intended patient population is well characterised, non-clinical *in vitro and in vivo* work can be performed using cell lines that can recapitulate key mutations or deletions that will be present in the clinic and compared with cell lines lacking these

[‡] http://www.science.cancerresearchuk.org/funding/apply/additional-information/biomarkers-imaging-definitions/.

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changes. If already characterised during the *in vitro* stage of non-clinical development, biomarkers can provide a key endpoint in rationally optimising dosing schedule prior to translation into man (although flexibility in clinical schedule is also required).

Although xenograft-bearing mice are the workhorse of cancer drug development, these models do have flaws which become more problematic as agents become more targeted. Xenograft models have rapid growth, no (or little) immune system, a xenological tumour:stroma interface and rarely metastasise, which can limit their use as models of human cancers. For many classes of anticancer agents (e.g. immunomodulatory or antimetastatic agents) xenografts should be seen as a stepping stone to more-representative models, whether syngeneic or transgenic. In such cases translation to the clinic based on xenografts alone carries significant developmental risks.

Translational considerations

For translation to the clinic a good understanding of the pharmacokinetic/pharmacodynamic (PK/PD) relationship is essential not just in plasma but also in the tumour itself. In clinical trials, obtaining tumour PK is challenging so an understanding of the plasma:tumour PK relationship at the non-clinical stage can be valuable. As the tumour is also the site of action for the majority of cancer therapeutics and delivery of a drug to the tumour is a key consideration in translation. The study of PD within the tumour models offers a key endpoint in the transition to *in vivo* studies and also offers an opportunity to examine peripheral surrogates of PD that might be translated to the clinic and, if validated, enable rapid transition away from the requirement for tumour biopsies. An early knowledge of the relationship between plasma and tumour drug concentration and the magnitude and persistence of response can facilitate a scientifically justified clinical schedule rather than relying on non-clinical schedules alone [11]. The use of *in vivo* imaging endpoints also offers great potential for non-invasive study of the effects of anticancer agents on the tumour directly [12].

Within cancer drug development there has been a growing focus on patient stratification and, although this has been seen as a purely clinical activity, initiating the search for possible stratification biomarkers early in development can enable, at the very least, patient enrichment to take place as early as Phase I [11,13]. Such stratification can increase the chances of patient benefit and minimising the exposure of patients to drugs unlikely to have efficacy in that individual. A great deal of genomic, proteomic and even metabolomic information is available for the cell lines in common cell screens, which can enable early correlations to be drawn between sensitive cell lines and key genetic changes. The identification of such markers of sensitivity has generated a great deal of success in early phase trials – for example ALK fusion in non-small cell lung cancer (NSCLC) [14] and v-raf murine sarcoma viral oncogene homolog B1 (BRAF) V600E in melanoma [15].

Safety studies

ICH S9 encourages a thoughtful scientifically justified approach to toxicology that requires non-clinical safety to be much more integrated into pharmacology, non-clinical efficacy and clinical trial design than has often been the case. One way to bridge the existing gap between safety and efficacy studies is to obtain additional safety information from efficacy studies by taking tissues for histopathology and blood for haematology and/or clinical chemistry rather than concentrating only on body weight and condition as safety endpoints. This has the additional benefit that efficacy and tolerability can be demonstrated in the same animal, which gives confidence for translation. This approach also enables safety data to be obtained in tumour-bearing animals which represent more-relevant models for human cancer patients. The risk mitigation guideline indicates that 'studies performed in animal models of disease may be used as an acceptable alternative to toxicity studies in normal animals'. Such combined safety/efficacy studies could therefore have the potential, at least in some circumstances, to replace work in a toxicological species altogether.

One welcome clarification in ICH S9 is that stand-alone safety pharmacology studies are only required in cases of particular concern. This encourages the use of additional endpoints within toxicity studies and discourages the automatic inclusion of unneeded studies – which helps reduce animal usage prior to FIH and speed translation. The exact criteria necessary for stand-alone studies is not stated, which puts the onus on the toxicologist to consider the risks posed and make scientifically justified case-by-case decisions – again an approach to be welcomed. In general the guideline encourages a risk mitigation approach in agreement with the risk mitigation guideline [4].

Implications for FIH cancer clinical trials

Risk mitigation and starting dose

The translation of non-clinical data to the clinic is not and cannot be an exact science and it needs be recognised that it can never be wholly predictive of the results of a clinical trial. Attempting to mitigate all risks non-clinically is never going to be possible nor should it be attempted. However, at present a great deal of work is performed non-clinically without such considerations taking place and, as a result, many non-clinical studies are carried out that might have little or no impact on the clinical mitigation strategies put in place. A judgement therefore needs to be made as to whether to address a risk non-clinically or to put adequate precautions into the protocol to mitigate that risk at the clinical stage. For some risks, on a case-by-case basis, risk mitigation directly in the clinical trial (with appropriate mitigation strategies in place) might be the preferable option and is encouraged by recent guidelines [3,4]. The justification for such an approach would, of course, have to be made clear in a regulatory submission.

Calculation of the starting dose in a first-time-in-human trial is a central factor affecting the safety of the subjects in a clinical trial. The goal of selecting the starting dose in trials in cancer patients, especially those with advanced cancers, is to identify a dose that is expected to have pharmacologic effects and is reasonably safe to use. The starting dose should be scientifically justified using all available non-clinical data and its selection based on various approaches. Although originally proposed primarily for biological agents, the minimum anticipated biological effect level approach can also have a great deal of value in selecting the starting dose for small-molecule agents. Justification should be given for the starting dose selected using each approach and the rationale for rejecting any lower doses.

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In general, unlike most other therapeutic areas, the highest dose or exposure tested in the non-clinical studies will not limit the dose-escalation or highest dose investigated in a clinical trial in patients with advanced cancer. When a steep dose- or exposure-response curve for a severe toxicity is observed in the non-clinical toxicology studies, or when no preceding marker of severe toxicity is available, smaller than usual dose increments (fractional increments rather than dose doubling) should be considered. It is always recommended that approaches outlined in the EU guideline on risk mitigation in FIH trials [4] are considered when designing trials in advanced cancer indications.

One of the keys to successful translation is flexibility in protocol design. Rigid schedules, dose escalations and PK/PD time points can restrict the freedom of early phase clinicians to act on emerging trial findings rapidly and this can reduce the value of data collected. This can be disadvantageous to the translation of the drug and to the safety of the patient. Flexibility also encourages rapid turnaround of PK/PD data and a more holistic approach to dose-escalation decisions – rather than merely relying on safety assessments alone.

Choice of endpoints in FIH trials

To date, clinical trials in cancer have primarily focused on dosing to MTD. Although this approach was ideal for cytotoxic agents, is it still appropriate for molecularly targeted agents? Certainly, this approach is often rejected in biological and immune therapies where maximum dose is usually estimated *via* biological endpoints. However, for many small molecules MTD is still seen as the most appropriate regimen because additional efficacy can be seen at secondary targets or efficacy prolonged owing to increased tumour penetration. Highly targeted agents are far less likely to have off-target activity, may rely on their selectivity for tolerability, have toxicity as a function of excess on-target pharmacology or have a safety profile that might suggest an MTD approach is inadvisable. In such cases dosing to a biologically effective dose or a plateau in biological effect might be preferable. In addition, in these cases biomarkers for on-target and downstream effect become crucial, although there is the problem of validation, for example if these markers are relatively new will they be appropriately characterised to make decisions about dose escalation?

Although there is now a draft position paper on the analysis of clinical trial samples [16] the status required for biomarkers to be used for patient stratification or biological dosing endpoints might prevent this from being used. How can the exposure of patients to excessive doses be balanced against decisions made on relatively poorly characterised endpoints? At present this is largely handled with patient 'enrichment' rather than stratification and dose escalation based on covert biomarkers as part of 'all available data' rather than stated overtly. A clarification of the level of characterisation required for making these decisions in early trials would be welcome.

Concluding remarks

The recent changes in guidelines relating to oncology represent a golden opportunity for more-rapid translation of therapies to the clinic. To date this opportunity has not been fully exploited.

For successful translation to the clinic a sound understanding of safety and efficacy is required, which necessitates a far greater integration of pharmacology and toxicology together with a well thought through scientifically justified approach to risk mitigation.

To understand the results of early phase trials a sound understanding and *in vivo* measurement of expected pharmacodynamics are fundamental. This can enable a well designed Phase I trial that addresses safety and efficacy questions.

If fully employed the recent changes to the guidelines regarding clinical trials in oncology should enable rapid translation and clinical evaluation of novel compounds. This approach should greatly accelerate drug development, providing adequate measures are put in place to inform developmental decisions and ensure patient safety.

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