ADMET & DMPK ***1****(4) (2013) 63-75; doi:* ***10.5599/admet.1.4.10***

ADMET

Open Access : ISSN : 1848-7718

http://www.pub.iapchem.org/ojs/index.php/admet/index

Mini Review

Estimating the "First in human" dose – a revisit with particular emphasis on oncology drugs

Kin Tam

Faculty of Health Science, University of Macau, Macau, China

E-mail: kintam@umac.mo; Tel.: +853-8397-8444; Fax: +853-8397-8500

Received: June 30th, 2013; Revised: October 21st, 2013; Published: December 16, 2013

Abstract

The initial dose selection is one of the important steps for any investigative new drug (IND) entering the first clinical study in humans. In this mini review, we will discuss the no observed adverse effect level (NOAEL) and the minimum anticipated biological effect level (MABEL) approaches for the estimation of the first in human (FIH) dose. Particular attention will be placed on the development of the FIH dose for oncology drugs.

Keywords

Initial dose; starting dose; clinical trial; NOAEL; MABEL; cytotoxic; anticancer; combination therapy study

1. Introduction

Estimating the first in human (FIH) dose is one of the initial steps in the clinical development of any molecule that has successfully gone through all of the hurdles in preclinical evaluations. It is an important parameter in the FIH clinical trials, since a high starting dose may cause serious toxicity in volunteers, while a low starting dose could prolong the dose escalation/optimisation, leading to unnecessary delay in the clinical programs. Adverse drug reactions do occur in clinical trials [1]. It is unethical to expose human subjects to poorly executed trials [2]. Clearly, protecting the volunteers is paramount, especially in the first human trial using healthy individuals.

Designing the appropriate FIH dose requires close collaboration among the pharmacokineticists, toxicologists, and preclinical scientists. Data from preclinical experiments such as animal, modelling, and pharmacokinetic data help to determine the initial dose and dosing interval in early clinical development. In 2005, the US Food and Drug Administration (FDA) issued guidance on estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers, which provided a framework to carry out the estimation [3]. Typically this involves the use of the no observed adverse effect level (NOAEL) obtained from preclinical toxicology studies, which is then converted into a human equivalent dose (HED) from which a safety factor is applied to derive the maximum recommended start dose (MRSD).

The NOAEL method is based on selecting a dose with minimal risk of toxicity, rather than selecting one with minimal pharmacology activity in humans. The approach appears to work well with new molecules that act on established targets and/or have pharmacology that is more or less understood. However, the life-threatening adverse events that occurred in 2006 after the FIH administration of TNG1412 (a novel CD28 super-agonist antibody) was a wake-up call to the industry, and led to immediate reactions from different regulators [4]. Subsequently, the European Medicines Agency (EMEA) has issued new guidance [5], which underlines the need to better mitigate the risk regarding FIH dosing, and proposes an improved approach to dose selection through the combined analysis of all of the pharmacology, safety and efficacy preclinical data. One of the main objectives of the new process is to define a starting dose that is expected to result in a minimum anticipated biological effect level (MABEL), particularly for investigational medicinal products where risk factors were identified in (1) mode of action, (2) nature of the target and (3) relevance of animal species and models.

With regard to oncology drugs, they are somewhat different from other therapeutic agents in terms of clinical evaluations and estimating the FIH dose. For example, the FIH clinical studies for traditional cytotoxic agents are usually carried out in patients with treatment-refractory cancer instead of healthy volunteers. In these instances, there is always a hope for a therapeutic benefit and a desire to minimise patient exposure to sub-therapeutic doses. The initial dose selection is usually based on the lethal dose in 10 % of animals (LD_{10}) [6]. There are additional considerations in the design of FIH dose for molecular targeted anticancer compounds.

In this article, we will first discuss the general considerations on FIH dose in the context of clinical trials. Then, we will briefly outline the NOAEL and the MABEL approaches for the estimations of FIH dose. Particular attention will be placed on the development of FIH dose for oncology drugs.

2. Entering the clinics

The main goal of clinical trials is to evaluate whether the treatment is effective and safe in humans. Before an investigational new drug (IND) can be given to humans, it must be tested thoroughly in animals to find out the following [7]:

(1) the effects in the body systems (pharmacodynamics (PD)),

(2) the blood levels and how it is absorbed, distributed, metabolised and eliminated after dosing (pharmacokinetics (PK)),

(3) a range of doses of the IND, up to a toxic level, the organ toxicity, and safety margin in terms of the NOAEL.

After the preclinical studies, there are four phases of trials in humans, which sometimes overlap in practice. Phases 1 to 3 are performed before a licence is granted, while Phase 4 is launched after authorisation [8]. Table 1 summarises the four clinical phases of the development of a typical drug.

Table 1. *Summary of the four clinical phases of development of a typical drug*[*]

Phase	*Typical number and type of subjects*	*Objectives*
1	*20 – 200 healthy subjects (usually) or patients who are not expected to benefit from the IND*	*Determine how well the IND can be tolerated in humans, study the clinical pharmacology and toxicity and find the maximum-tolerated dose to aid the selection of dose and/or schedule for Phase 2*
2	*100-400 patients with the target disease*	*Examine dose–response curves in patients, and evaluate the clinical benefits that might be seen in a small group of patients*
3	*1000-5000 patients with the target disease*	*Test in a controlled fashion in a large patient population against a placebo or standard therapy with respect to safety and efficacy*
4	*Many thousands of patients with the target disease*	*Post-marketing study to gather additional safety information from a larger group of patients in order to understand the long-term safety and monitor drug-drug interactions*

[*] *The number of subjects listed in the table were adopted from the ABPI guidelines [9]. It should be noted that these values could vary, depending on the therapeutic areas, the trial design and the clinical questions to be addressed. For any clinical trial, the number of subjects has to be planned on a justifiable and rational basis (see reference 10 for further detail).*

Before an IND enters a Phase 1 trial, one of the most important tasks is to estimate a starting dose that is low enough to be safe in humans, but not so conservative that excessively costly and time-consuming dose escalations are needed. Generally, the estimation is largely based on the pharmacology and toxicity data, while pharmacokinetics is a bridge of pharmacology and toxicity. However, the design of a dose escalation strategy in clinical studies is beyond the scope of this article. In the next section (section 3), we will discuss the approach endorsed by FDA for estimating the maximum safe starting dose in initial clinical trials.

3. The NOAEL approach for dose selection

There were different approaches that could be used to calculate the starting dose in FIH studies; to name a few: NOAEL from preclinical toxicology studies multiplied by a safety factor, the similar drug approach and the pharmacokinetically guided approach [11,12]. Estimating the optimal starting dose is complicated, especially when extrapolation of doses from animals to humans is based on multiple assumptions. Indeed, different methods may yield widely varying results [11]. There was no consensus regarding the best approach for estimating the starting dose. It was not until 2005, when the FDA issued their guidance [3], that the approach based on NOAEL and safety factor became the most common method for estimating the starting dose. In the following discussion, we will focus on the NOAEL approach. Readers who are interested in other approaches are directed to the relevant review papers for methodological details [11,12].

The FDA guidance outlines a standardised process for deriving the maximum recommended starting dose (MRSD) for adult healthy volunteers in Phase 1 studies [3]. The main steps of this process are: (1) the determination of the NOAELs in animal species, (2) the conversion of NOAELs to the human equivalent dose (HED) using the allometric scaling factors listed in Table 2, (3) selection of the most appropriate animal species, and (4) the application of a safety factor to derive the MRSD.

Table 2. *Conversion factors of animal doses to human equivalent doses [3]*

Species	*To convert animal dose in mg/kg to HED mg/m^2, multiply by $k_m$$^+$*	*To convert animal dose in mg/kg to HED* in mg/kg, either:*	
		Divide animal dose by	*Multiply animal dose by*
Human	*37*		
Mouse	*3*	*12.3*	*0.08*
Hamster	*5*	*7.4*	*0.13*
Rat	*6*	*6.2*	*0.16*
Ferret	*7*	*5.3*	*0.19*
Guinea pig	*8*	*4.6*	*0.22*
Rabbit	*12*	*3.1*	*0.32*
Dog	*20*	*1.8*	*0.54*
Monkeys	*12*	*3.1*	*0.32*
Marmoset	*6*	*6.2*	*0.16*
Squirrel monkey	*7*	*5.3*	*0.19*
Baboon	*20*	*1.8*	*0.54*

* *Assumes 60 kg human. For species not listed or for weights outside the standard ranges, HED can be calculated from the following formula: HED = Animal Dose (mg/kg) × (Animal Wt. (kg)/Human Wt. (kg))$^{0.33}$*

$^+$ *Factor for converting mg/kg dose to mg/m^2 dose*

Step 1: NOAEL determination

This is the first step in the process, which involves the evaluation of the available animal data to determine the NOAELs from toxicology studies. Here, the NOAEL refers to the highest dose level that does not produce significant adverse effects compared with the control group. Biologically significant or PD effects are acceptable provided that they do not raise a safety concern. The adverse effects used to define the NOAEL should be based on an effect that would be unacceptable if produced by the initial dose in a Phase I clinical trial. The NOAEL for each toxicology study is usually reported in mg/kg.

Step 2: HED calculation

The NOAEL for each tested species should be determined, and then converted to the HED using appropriate scaling factors, as shown in Table 2. For systemically administered agents, the conversion should be based on the normalisation of doses to body surface area (assumed doses scaled 1:1 when

normalized to body surface area). There are exceptions where the mg/m^2 scaling between species is not expected to work well. These include: therapeutics administered by alternative routes (e.g., topical, intranasal, subcutaneous, intramuscular, intrathecal, intravesical, intraocular, or intrapleural) and proteins administered intravascularly. In such cases, alternative means of normalisation should be utilised [3]. Conversion of the animal NOAEL to the HED should be normalised to mg/kg. The species that generates the lowest HED is referred to as the most sensitive species.

Step 3: Selection of the most appropriate species

In the absence of any information to aid the selection of species to assess the risk in humans, the most sensitive species is then regarded as the most appropriate, since the use of the lowest HED would generate the most conservative starting dose. However, if there is information suggesting a particular species is more relevant for assessing the risk in humans, the HED of that species could be used.

Step 4: Application of safety factor

A safety factor should then be applied to the HED to provide a margin of safety for protection of human subjects receiving the initial clinical dose. The MRSD is obtained by dividing the HED by the safety factor; the default safety factor is 10. This is a historically accepted value, but should be evaluated based on available information. For instance, the safety factor should be increased in situations in which steep dose–response curve, severe/irreversible toxicities, unexplained mortality, variability in doses or drug levels eliciting effects, variable bioavailability, or nonlinear pharmacokinetics were seen in preclinical studies.

It can be seen that the MRSD was derived based on the adverse effects seen in preclinical toxicology studies. Near the end of the FDA guidance document [3], there is brief mention of the merits of comparing the MRSD with pharmacological active dose (PAD) derived from appropriate PD models, and adjusting/reducing the FIH dose accordingly. For certain classes of drug or biologics, the toxicity may arise from exaggerated pharmacologic effects, so the PAD could be a more sensitive indicator of potential toxicity. However, little details were given in the guidance document regarding the selection of PAD and the strategy for reducing the clinical starting dose.

4. The drug trial that went horribly wrong

In 2006, a Phase I clinical trial was conducted at Northwick Park Hospital in London to evaluate a humanised monoclonal antibody – a CD28 superagonist, also known as TGN1412 [4]. TGN1412 was in development for the treatment of B cell chronic lymphocytic leukaemia, with the expectation that it would reverse the T cell deficiency in this disease, by activating the T cell compartment [13]. Soon after the administration of TGN1412 to 6 healthy volunteers, the trial turned into a catastrophe because the treatment unexpectedly induced a rapid and massive cytokine storm that caused severe and life-threatening adverse effects in all six volunteers. Six volunteers were hospitalised and suffered from multiple organ dysfunction [4]. The drug was immediately withdrawn from development.

Extensive studies have been carried out to investigate the cause of this adverse side effect in humans [14-16]. Prior to the clinical trial, TGN1412 was tested in preclinical species for toxicology studies and did not show any obvious adverse effects [14]. There is still lack of evidence to explain why TGN1412 did not stimulate the profound cytokine release *in vitro* or *in vivo* in preclinical species used in safety testing. The underlying molecular mechanisms leading to the adverse reaction in humans are not yet fully understood. It is plausible that a species difference in the organisation and regulation of T cell responses is responsible for this disparate immunopharmacology [17,18]. Nevertheless, the TGN1412 study was the first trial of this

type of compound in human at the time and a small amount of published data were available before the clinical investigation. Similar clinical trials of antibodies against T cell antigens had already shown toxic effects [14], suggesting that the TGN1412 trial would be a high-risk study.

In the TGN1412 trial, the calculation of the starting dose was based on the NOAEL approach (section 3). A starting dose of 0.1 mg/kg was selected, which corresponded to 160 times lower than the HED derived from the cynomolgus monkey studies (assuming this species was most predictive for human). Subsequent analysis by the Expert Scientific Group reported that the trial was conducted according to the Medicines and Healthcare Products Regulatory Agency (MHRA) approved policy and there were no errors involved in the manufacture of TGN1412 or in its formulation, dilution or administration to trial participants [4]. It was then concluded that an unpredicted biological action of the drug in humans was the most likely cause of the adverse reactions. However, it has also been suggested that the tragic incident would have been an avoidable rather than an unforeseeable event if the clinical trial had been designed to emphasise the safety of the trial participants [19]. Instead of using the NOAEL approach, the report also highlighted the use of MABEL to estimate the FIH dose, which would result in a much lower value for TGN1412 – about 20-fold lower than the dose used in the trial. It may be possible that the use of a lower initial dose could avoid the adverse effect seen in the TGN1412 trial, but this is a hypothesis that one would never have the opportunity to testify. Nevertheless, after the publication of the Expert Scientific Group report, the EMAE has issued a guidance document that endorsed the use of the MABEL approach for estimating the FIH dose, especially for high-risk studies [5]. In the next session, we will briefly discuss the EMAE guideline that endorses the MABEL approach for dose selection.

5. The MABEL approach for dose selection

The EMAE guideline identifies factors influencing risk for new investigational medicinal products, which covers the transition from nonclinical to early clinical development [5]. Strategies for mitigating and managing risk are given. These include: the calculation of the first dose in humans, the subsequent dose escalation, and the conduct of the clinical trial, all of which are thought to have been triggered by the tragic incident of the TGN1412 trial. The guideline is supposed to use in conjunction with several other nonclinical and clinical EU guidelines. The non-clinical safety aspect is particularly emphasised with reference to the ICH M3 (non-clinical safety studies for clinical trials) [7] and the ICH M6 (preclinical safety evaluation of biotechnology-derived pharmaceuticals) [20], and four other related guidelines [5]. Here, we will direct our attention to the estimation of the first dose in humans.

As highlighted above, risk identification and risk mitigation are the focuses of this EMAE guideline. In particular, factors of risk may be derived from the lack of knowledge in the following areas:

(1) the mode of action

This refers to the knowledge on the nature and intensity of the effect of the medicinal product on the specific target and non-targets and subsequent mechanisms. Certain modes of action have been identified to require special attention, which include targets that have pleiotropic effects or are ubiquitously expressed (e.g., as often occur in the immune system) and those that have a biological cascade or cytokine release, including those leading to an amplification of an effect that might not be sufficiently controlled by a physiological feedback mechanisms (e.g., in the immune system or blood coagulation system). Monoclonal antibodies against the T cell targets are named as examples of products that have this latter type of mode of action, presumably because of the TGN1412 trial (see section 4).

(2) the nature of the target

This may include information on the structure, tissue distribution, cell specificity, disease specificity, regulation, polymorphisms, level of expression, and biological function of the human target, including downstream effects, and how it might vary between individuals in different populations of healthy subjects and patients.

(3) the relevance of animal models.

The available animal species should be compared to humans taking into account the target, its structural homology, distribution, signal transduction pathways and the nature of pharmacological effects. Where the available animal species/models or surrogates are perceived to be of questionable relevance for thorough investigation of the pharmacological and toxicological effects of the medicinal product, this should be considered as adding to the risk.

The EMEA guideline has pointed out that the risk assessment should be performed on a ‘‘case-by-case’’ basis and that a ‘‘weight-of-evidence’’ approach should be used. Despite the scope of the guideline covering both chemical and biological investigational medicinal products, the above factors of risk are mostly derived from the intended pharmacological mechanism (rather than from chemical mechanisms), which are more relevant to the exaggerated “on-target” pharmacology as the mechanism of toxicity for many biologics. In the calculation of the FIH dose, it has been suggested that all of the information has to be taken into consideration for the dose selection. In general, the NOAEL approach is still regarded as the method that gives the most important information. However, for investigational medicinal products where the above risk factors have been identified, the use of the MABEL approach is recommended. The calculation of MABEL should use all *in vitro* and *in vivo* information available from PK/PD, which may include the following:

(1) target binding and receptor occupancy studies *in vitro* in target cells from human and the relevant animal species

(2) concentration-response curves *in vitro* in target cells from human and the relevant animal species and dose/exposure-response *in vivo* in the relevant animal species

(3) exposures at pharmacological doses in the relevant animal species

To further limit the potential for adverse reactions in humans, a safety factor may be applied in the calculation of the first dose in humans from MABEL. This should take into account the criteria of risks such as the novelty of the active substance, its biological potency and its mode of action, the degree of species specificity, the shape of the dose-response curve and the degree of uncertainty in the calculation of the MABEL. In cases where the methods of calculation (e.g. NOAEL, MABEL) give different estimations of the first dose in man, the lowest value should be used.

There are challenges related to the calculation of the MABEL. For example, the guideline does not provide much detail on the criteria to define the minimal biological effect, the recommended value for the safety factor (if applicable), or any example of how MABEL could be calculated. Fortunately, the Expert Scientific Group report has given examples of MABEL calculations for TGN1412 and two other products, as well as the calculation of MABEL for TGN1412 based on receptor occupancy [4]. Following the publication of the Expert Scientific Group report, other papers on the use of the MABEL approach to estimate the initial dose for biologics have started to appear in open literature [21-26]. These would undoubtedly serve as examples for clinical investigators to select the FIH dose with the MABEL approach.

6. Initial dose selection for oncology agents

We now turn to the initial dose selection for anticancer drugs. In 2013, EMAE issued an updated guidance document on the evaluation of anticancer medicinal products in humans [27]. The document was adopted from early guidelines dating back to 1996, where the focus was mainly on cytotoxic anticancer compounds. In contrast to the previous version published in 2005, the guideline highlighted the importance of the exploratory clinical (Phase 1/2) studies to identify the most appropriate target population for treatment with the selected biomarkers, expanded the coverage on confirmatory trial (Phase 3 study), and emphasised the importance of understanding the pharmacokinetics, particularly in the potential of drug-drug interactions, and for patients with impaired organ function. The use of PK/PD analysis supported by biomarkers and clinical markers data in Phase 2/3 studies has been particularly encouraged.

The EMEA guideline loosely classified anticancer drugs as cytotoxic and non-cytotoxic [27]. Cytotoxic compounds elicit the anticancer effects by means of killing or preventing the division of cells. The drug action is nonspecific in targeting abnormal and normal cells, which is usually linked with toxicity. Classical cytotoxic chemotherapeutic agents include: the nitrogen mustard derivatives (e.g. cyclophosphamide, melphalan), antimetabolites (e.g. fluorouracil, methotrexate), platins (e.g. cisplatin, oxaliplatin), antimicrotubule agents (e.g. taxol, vinblastine) and antitumor antibiotics (e.g. doxorubicin, mitomycin C). As for non-cytotoxic anticancer compounds, this generally refers to molecular targeted agents where the drug activity may connect with novel mechanisms such as hormones, nuclear-targeting, and signal-transduction targeting. Molecular targeted anticancer compounds have the capacity to modify target or receptor function in an ongoing manner, and are usually less toxic. This kind of behaviour can be exemplified by the hormone receptor-directed agents (e.g. tamoxifen, anastrozole) and many onocogene-directed kinase inhibitors such as gefitinib, erlotinib, imatinib, dasatinib, and sorafenib. Immune modulators/monoclonal antibodies (e.g. bevacizumab, cetuximab) and combination therapy studies are regarded as two separated categories of anticancer products in the guideline.

Owing to the differences in drug actions among the cytotoxics and non-cytotoxics (molecular targeted compounds), and immune modulator/monoclonal antibody and combination therapy studies, the approaches for initial dose selection are varied considerably. In the following discussion, we will discuss the FIH dose selection approaches for these four classes of treatments.

6.1. Cytotoxics

The cytotoxic compounds induce irreversible lethal cellular lesions following short-term exposure, which are relatively nonselective in terms of their effects on tumours against normal cells. For these compounds, toxicity and tumour response can be regarded as suitable indicators of drug activity [27]. Because of their inherent toxicity, the clinical trials of cytotoxic agents are not conducted in healthy volunteers. Instead, the FIH trial of these agents usually involves patients with advanced incurable malignancy, which differs considerably from those in most other therapeutic areas. Selection of the starting dose for the initial Phase I clinical trial of cytotoxic oncology drug is based on animal toxicology studies [6,27]. These studies are typically performed in rodents (e.g. mice/rats) or other non-rodent large species (e.g. dogs). It has been shown that rodent-only toxicity study (with mice and rats) was sufficiently predictive in identifying the Phase I trial starting dose and commonly encountered dose-limited toxicities [28]. This suggests that the routine use of a non-rodent large species in preclinical toxicology studies prior to initial clinical trials with cancer therapeutics is not always necessary. From the mice studies, the dose at which 10% of the mice die (the murine LD_{10}) is defined. One-tenth of this value, 0.1 MLD_{10}, expressed in

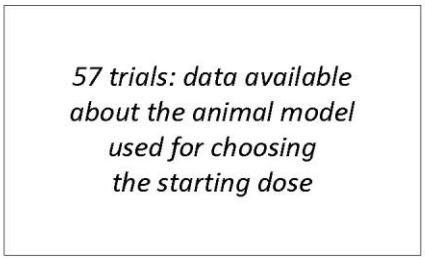
mg/m^2, has been historically regarded as a safe starting dose in humans provided that the toxicology studies in a second species (e.g. dog) did not show serious, irreversible toxicity and substantial differences in the dose–toxicity relationship [29]. If irreversible toxicities are produced at the proposed starting dose in non-rodents or if the non-rodent is known to be a more appropriate model, then the starting dose could be based on one-third of the lowest dose in non-rodents that produces drug-induced pathological alterations in haematological, clinical, or morphological parameters and which, when doubled, produces no lethality [11]. Readers are directed to a literature working example of designing the safe starting dose for a cytotoxic agent for further methodological details [30].

However, ethical concerns exist on using excessive numbers of patients at sub-therapeutic doses of a new cytotoxic agent to reach the maximum-tolerated dose (MTD) during dose escalation [29]. Increasing the starting dose and/or pursuing a more aggressive dose escalation schedule could potentially reduce the number of patients treated at sub-therapeutic doses. On the other hand, it is important to protect patients from unacceptable risk in terms of toxicity. There is a fine balance between the starting dose selection, escalation strategy and patient safety.

6.2. Non-cytotoxics (molecular targeted compounds)

Unlike cytotoxic drugs, the pharmacological effects of molecular targeted compounds rarely induce acute cellular damage. Most often, these drugs are cytostatic, and are likely to be more effective when administered continuously. Usually, molecular targeted compounds will interact with proteins that are specific to tumour cells or that are up-regulated during malignant transformation. Thus, they tend to be more selective and less toxic to normal tissue. Increasing the dose in a traditional Phase 1 trial to the MTD may be irrelevant for molecular targeted compounds as the maximum therapeutic effect may be achieved at doses that are well below the MTD. In some situations, it may be difficult to determine the MTD [31]. As such, the early stages of clinical drug development are likely to be more complex and have to be tailored according to the assumed pharmacology of the compound as defined in preclinical studies. An early assessment of anti-tumour activity using biomarkers and PD (e.g. receptor binding, enzyme inhibition, downstream events, or sensitive imaging techniques) may be required to help to define the dose and schedule.

For molecular targeted compounds, there does not appear to be a standardised approach for selecting the FIH dose. This is not even mentioned in the EMEA guideline [27]. Indeed, Le Tourneau et al. reported that there is no consensus on which preclinical models and parameters should define the starting dose for molecular targeted compounds [31]. The authors have analysed 81 FIH Phase I trials that evaluated 60 different molecular targeted agents; the data were taken from open literature from 1998 to 2009. In the 81 trials, 57 of which have clearly specified the animal models used to derive the starting dose. Figure 1 shows the preclinical models and toxicological parameters used to derive the starting dose of these 57 Phase I clinical trials of molecular targeted compounds. It can be seen that the selections of FIH dose were based on diverse practices using a variety of preclinical toxicological parameters. Nevertheless, most of these trials appeared to be safely conducted, which is consistent with the fact that toxicity may not be a critical issue in molecular targeted compounds, as compared with cytotoxic anticancer compounds.



Choice of the starting dose based on rodents	Trials
1/10 x MTD or LD_{10}	16
1/30 x LD_{10}	1
[1/10-1] x TDL	6
[1/10-1/3] x NOAEL	2
[1/20-1/10] x STD_{10}	2
1/10 x STD	1
1/10 x STD	1
Total	29

Choice of the starting dose based on nonrodents	Trials
1/10 x MTD	2
1/6 x MTD	4
1/20 x LD_{10}	1
[1/25-1/3] x TDL	9
[1/6-1/5] x NOAEL	4
1/10 x STD	1
1/6 x MED	1
Not specified	6
Total	28

Figure 1. *The preclinical models and toxicological parameters used to derive the starting dose of the 57 Phase 1 cancer clinical trials of molecular targeted compounds (adapted from reference 32). MTD, maximum-tolerated dose; LD_{10}, lethal dose for 10% of animals; TDL, toxic dose low; NOAEL, no observed adverse event level; STD_{10}, severely toxic dose for 10% of animals; MED, minimum effective dose.*

6.3. Immune modulators and monoclonal antibodies

For these kinds of compounds, it has been suggested that the selection of starting dose may be supported by the MABEL approach, as discussed in Section 5 [27].

6.4. Combination therapy studies

Cytotoxic compounds have been used in combination to increase the anti-tumour activity at acceptable levels of toxicity. This may be accomplished by combining compounds with at least partly non-overlapping toxicity, activity or resistance. However, it may be difficult to predict whether this kind of combination therapy would lead to a better treatment outcome than the individual agents that are consecutively used in isolation. In combining two conventional cytotoxic compounds, it may be possible to predict the toxicity based on the toxicities of individual components. Assuming that the PK interactions of the two compounds

are negligible, the starting dose could be about one half of the recommended mono-therapy dose for each compound [27]. If the hypothesised interaction would lead to an anticipated increased drug exposure, the first dose-level should be cautiously low. Alternatively, it may be reasonable to start at the recommended dose for one compound and a reduced dose (<50%) of the other.

In cases where at least of one the two components is a non-cytotoxic compound, it is desirable to have compelling preclinical rationale to support the combination study [33]. This kind of combination Phase 1 study is very complex. The Methodology for the Development of Innovative Cancer Therapies (MDICT) task force has recently published a paper concerning recommendations on combination therapy studies [34]. With regard to the schedule and dose, the paper simply remarked that they "should be formally explored for e.g. with a randomised or adaptive design". As far as we are aware, little, if any, information is available in open literature describing the estimation of starting dose and clinical trial design in this kind of study. Given the high uncertainty to predict the add-on activity in non-clinical models, the EMEA has recommended the incorporation of randomised Phase 2 studies to compare the experimental regimen with the chemotherapy-alone regimen [27].

7. Conclusions

Estimation of the FIH dose is one of the important steps in Phase 1 clinical trials. The initial human dose has to be low enough to ensure the safety of the human participants, but not so conservative that excessively costly and time-consuming dose escalations are needed. The NOEAL approach endorsed by the FDA [3] is a commonly used method to perform the initial dose prediction. This is based on the data obtained from preclinical toxicology studies. Following the tragic incident of the TGN1412 Phase 1 trial, it has been recognised that the NOEAL approach might not be sufficient to provide a safe initial dose estimate, especially for high-risk investigative medicinal products that the mechanisms of the pharmacological actions in human are not fully understood. Since then, the EMEA has endorsed the MABEL approaches [5] for estimating the FIH dose of high-risk investigative medicinal products. This comprehensive approach made use of all preclinical *in vitro* and *in vivo* information available from PK/PD, which appears to provide a more conservative estimate of the initial dose on many occasions. This is particularly useful for biologics and/or high-risk investigative medicinal products where the toxicity is closely related to the exaggerated "on-target" pharmacology.

With regard to oncology drugs, they are somewhat different from other therapeutic agents in terms of clinical evaluations and estimating the FIH dose. The recently published EMEA guideline [27] provided up-to-date recommendations in the clinical study of oncology products, which include: cytotoxics, non-cytotoxics, immune modulator/monoclonal antibody and combination therapy studies. It is noted that the FIH dose estimation for cytotoxics is usually based on a fraction of the lethal dose obtained from preclinical toxicology studies. For immune modulator/monoclonal antibodies, the MABEL approach is recommended. As for non-cytotoxics, the selection of FIH dose was based on diverse practices. As far as we are aware, there is currently no established protocol or consensus regarding the FIH dose selection in combination therapy studies involving molecular targeted compound(s). This reflects on the complex nature of the clinical trial design for this kind of combination study, which would have to consider a "case-by-case" basis.

References

[1] S. Derry, Y.K. Loke, J.K Aronson, *BMC Medical Research Methodology* **1** (2001) 7.

[2] D.L. Streiner, *Canadian Journal of Neurological Sciences* **34: S1** (2007) S37-S41.

[3] FDA Guidance for industry - Estimating the maximum safe dose in initial clinical trials for therapeutics in adult healthy volunteers 2005, http://www.fda.gov/downloads/Drugs/Guidances/UCM078932.pdf (accessed 19 June, 2013)

[4] Expert scientific group on Phase one clinical trials final report 2006, http://www.tfscro.com/business/doc/Final_Report_of_the_Expert_Scientific_Group_(ESG).pdf (accessed 19 June, 2013)

[5] EMEA Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products 2007, http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002988.pdf (accessed 19 June, 2013)

[6] J.J. DeGeorge, C.H. Ahn, P.A. Andrews, M.E. Brower, D.W. Giorgio, M.A. Goheer, D.Y. Lee-Ham, W.D. McGuinn, W. Schmidt, C.J. Sun, S.C. Tripathi, *Cancer Chemotherapy and Pharmacology* **41** (1998) 173-185.

[7] ICH guidelines M3 (R2) on Non-clinical safety studies for clinical trials 2009, http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002720.pdf (accessed 20 June, 2013)

[8] D. Wang, A. Bakhai, *Clinical Trials- A Practical Guide to Design, Analysis and Reporting*, Remedica, London, UK, 2006.

[9] Guidelines for Phase I Clinical Trials 2007, http://www.abpi.org.uk/our-work/library/guidelines/Documents/phase1-trial-guidelines.pdf (asccessed 12 October, 2013)

[10] B. Röhrig, J.B. du Prel, D. Wachtlin, R. Kwiecien, M. Blettner, *Deutsches Ärzteblatt International* **107** (2010) 552-556.

[11] B.G. Reigner, K.S. Blesch, *European Journal of Clinical Pharmacology* **57** (2002) 835–845.

[12] I. Mahmood, M.D. Green, J.E. Fisher, *Journal of Clinical Pharmacology* **43** (2003) 692-697.

[13] T. Hünig, *Advances in Immunology* **95** (2007) 111–148.

[14] M.J.H. Kenter, A.F. Cohen, *Lancet* **368** (2006) 1387–1391.

[15] Z. Waibler, L.Y. Sender, C. Merten, R. Hartig, S. Kliche, M. Gunzer, P. Reichardt, U. Kalinke, B. Schraven, *PLoS ONE* **3(3)** (2008) e1708

[16] D. Eastwood, L. Findlay, S. Poole, C. Bird, M. Wadhwa, M. Moore, C. Burns, R. Thorpe, R. Stebbings, *British Journal of Pharmacology* **161** (2010) 512–526.

[17] B. Schraven, U. Kalinke, *Immunity* **28** (2008) 591-595.

[18] N. Müller, J. van den Brandt, F. Odoardi, D. Tischner, J. Herath, A. Flügel, H.M. Reichardt, *Journal of Clinical Investigation* **118** (2008) 1405-1416.

[19] C.J. Horvath, M.N. Milton, *Toxicologic Pathology* **37** (2009) 372-383.

[20] ICH guidelines S6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals 2011, http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002828.pdf (accessed 24 June, 2013).

[21] P.J. Lowe, Y. Hijazi Y, O. Luttringer, H. Yin, R. Sarangapani, D. Howard, *Xenobiotica* **37** (2007) 1331-1354.

[22] B.M. Agoram, *British Journal of Clinical Pharmacology* **67** (2008) 153–160.

[23] P.Y. Muller, M. Milton, P. Lloyd, J. Sims, F.R. Brennan, *Current Opinion in Biotechnology* **20** (2009) 722-729.

[24] P.J. Lowe, S. Tannenbaum, K. Wu, P. Lloyd, J. Sims, *Basic & Clinical Pharmacology & Toxicology* **106** (2009) 195–209.

[25] J.P. Gibbs, *The AAPS Journal* **12** (2010) 750-758.

[26] J. Yu, H. Karcher, A.L. Feire, P.J. Lowe, *The AAPS Journal* **13** (2011) 160-178.

[27] EMEA Guideline on the evaluation of anticancer medicinal products in man 2012, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/01/WC500137128.pdf (accessed 26 June 2013).

[28] D.R Newell, S.S. Burtles, B.W. Fox, D.I. Jodrell, T.A. Connors, *British Journal of Cancer* **81** (1999) 760–768.

[29] E.A. Eisenhauer, P.J. O'Dwyer, M. Christian, J.S. Humphrey, *Journal of Clinical Oncology* **18** (2000) 684-692.

[30] A.M. Senderowicz, *Clinical Cancer Research* **16** (2010) 1719-1725.

[31] N. Saigo, T. Tamura, K. Nishio, *Cancer Chemotherapy and Pharmacology* **46** (2000) S43-S45.

[32] C. Le Tourneau, A. Stathis, L. Vidal, M.J. Moore, L.L. Siu, *Journal of Clinical Oncology* **28** (2010) 1401-1407.

[33] J. Verweij, M.L. Disis, S.A. Cannistra, *Journal of Clinical Oncology* **28** (2010) 4545-4546.

[34] L.K. Seymour, A.H. Calvert, M.W. Lobbezoo, E.A. Eisenhauer, G. Giaccone, *European Journal of Cancer* **49** (2013) 1808-1814.