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Review Article

A review of first-in-human small molecule oncology clinical trials

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ABSTRACT

First-in-human (FIH) oncology clinical trials are crucial to the development of small-molecule oncology candidates. However, there is a dearth of research investigating how these trials vary from one-another and therefore whether one approach may be better than another. This review aims to investigate variation of FIH trials published over the last decade with respect to four areas: publication particulars; trial design; patient particulars and drug administration and formulation.

Keywords: First-in-human, Oncology, Cancer, Clinical trials, Small molecule

INTRODUCTION

Cancer continues to be one of the most common causes of death globally. According to the International Agency for Research on Cancer, there were nearly 14.1 million new cancer diagnoses worldwide in 2012 with 57% in less developed regions and 43% in more developed regions.[1] In the same year cancer was responsible for 8.2 million deaths with a greater mortality rate in less developed regions when compared with more developed regions, 66.4% vs. 47.5%.[1] Most alarmingly, the incidence of cancer is expected to rise by around 70% over the next two decades.[2] These statistics highlight the urgency, more than ever, for new oncology medicines.

First-in-human (FIH) oncology trials, those where a drug candidate is given to humans for the first time, are crucial to the development of new evidence based medicines. Despite this, a systematic analysis of 8,942 oncology trials in 2013 concluded that there are significant variations in the design of oncology clinical trials; variations that need to be better understood to improve the impact of cancer research and make the process more economical.[3] FIH clinical trials can be phase 0 or I studies. In phase 0 trials, a sub-therapeutic dose is administered, typically to learn about absorption, distribution and metabolism as well as determining pharmacodynamics parameters. In phase I trials, doses are administered primarily to gain an understanding of safety and toxicity, with the aim to determine the dose for taking the compound forward into the next stage of a clinical trial. According to Tourneau et al "the guiding principle for dose escalation in phase I trials is to avoid exposing too many patients to sub-therapeutic doses while preserving safety and maintaining rapid accrual".[4] This principle of preserving safety echoes the declaration of Helsinki, which states that medical research should protect the health of patients.[5]

Due to the cytotoxic nature of many small molecule oncology candidates, the primary endpoint for these trials is often toxicity; this being where patients at a particular dose experience a toxicity of significant severity to stop further dose escalation, as determined by the trial protocol.[4] This is defined as the 'dose limiting toxicity' (DLT), with the preceding dose level often being described as the maximum tolerated dose (MTD) and typically the recommended phase II starting dose.[4] Despite a surge in the research and development of biologically targeted oncology therapies (biologics) over the last decade, small molecules are more commonly investigated in clinical trials; of 352 drugs in phase I

trials in February 2014, 59% were investigating small molecules whilst 41% focused on biologics.[6]

As far at the authors are aware, there has been no review in the last decade of first-in-human oncology clinical trials of small molecule candidates. Here we have reviewed 69 FIH trials to describe and analyse variations in their publication, design, participants, and information on drug formulation and administration used.

METHODS

Literature detailing first-in-human trials of small molecule oncology candidates was sought through searching the online databases PubMED, Web of Science and Wiley Online library. The search keywords used were: (1) 'first-in-man' [title] OR (2) 'first-in-human' [title] OR (3) 'oncology OR cancer'. A further search was completed which replaced keywords (1) and (2) with (4) 'dose escalation'. The search keyword 'phase I' was considered, however preliminary searches returned a large number of publications which were not true first-in-human clinical trials or for which this was difficult to determine. Searches were limited to trials published between 01 January 2005 and 20 March 2015, the date the final search was completed.

A total of 69 trials applicable to the aim of this review were identified.[7-75] Each paper was reviewed individually and, where available, information extracted and collated. These data were then used to investigate the areas detailed below. Variables have been compared using a two-tailed t-test with 95% confidence intervals.

Publication particulars

Four components in relation to the publication of FIH trials have been assessed: country of corresponding author; year of publication; sponsor and journal of publication.

Trial design

The following components of trial design have been explored: method of dose escalation; intra-patient dose escalation; blinding; number of arms; determining dose increments; and the number of unique dose levels.

Participant particulars

The number of patients enrolled to each trial was recorded; this is not necessarily the number of patients who participated due to the possibility of patient withdrawal following the screening process. Data specific to patients' disease status has been considered; namely, their eastern cooperative oncology grading (ECOG) and primary diagnosis. Due to the vast number of possible cancer diagnoses, data for patients diagnosed with one of 27 cancers of greatest global incidence and mortality (the same 27 cancers) were grouped, with diagnoses falling outside of these groups being classed as 'other'. The 27 cancers of greatest incidence and mortality were chosen based on data from Cancer Research UK.[76,77]

Drug administration and formulation

The administration route used to dose patients as well as the particular formulation used to administer have been determined.

DISCUSSION

Of the 69 trials reviewed, 64 were of parallel multiple dose design (PMD) with the remaining five being parallel single dose (PSD). In order to allow for more meaningful comparison, PMD and PSD trials have been analysed individually; sections 1-4 below focus on PMD trials and section 5 focuses on PSD trials.

Publication particulars

The majority of the 64 PMD studies (47%) have their corresponding author located in the United States. This supports the well-established fact that the United States are significant contributors to clinical oncology research, spending more than any other region[78].

Within the remit of this review, the number of FIH trials published over the last decade has increased year-on-year. This may reflect an increase in oncology research and/or funding, limitations in the function of literature databases, changes in the nomenclature of FIH trials or a general increased tendency to publish clinical trials in peer-reviewed journals. Figure 1 summarises publications by year and country of corresponding author over the last decade.

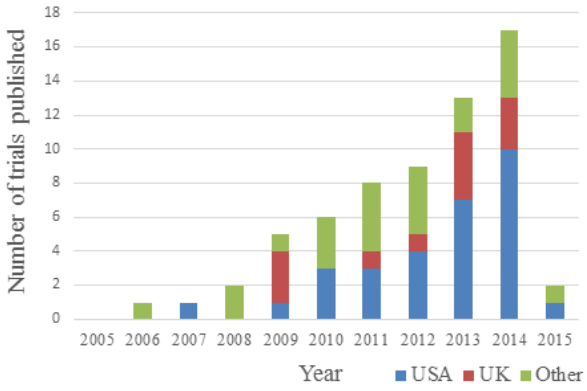

Figure 1: Distribution of trials by year published and country of corresponding author.

Sixty-one studies (95%) published their trial sponsorship with 54 (89%) being privately funded by a pharmaceutical company, 4 (7%) receiving public funding and 3 (5%) being jointly funded between public and private organisations. If FIH trials published are a

reflection of trials conducted, this indicates that industry fund the vast majority of FIH studies. Of all industry-funded trials, including collaborations between companies, 48 companies sponsored at least one trial; Boehringer Ingelheim, Merck & Co., Inc., Astex and PharmaMar contributed towards two; while GSK, Novartis and Pfizer contributed towards three. Bayer (including those studies published under its previous name of Bayer-Schering) was the only industry sponsor to contribute towards four trials.

Some peer-reviewed journals were a more popular choice for publication than others. 'Clinical Cancer Research' was the most popular journal chosen for publication with 22 trials. 'Cancer Chemotherapy and Pharmacology' and the 'European Journal of Cancer' were the next most popular with 11 and 8 trials respectively.

Trial design

Method of dose escalation

Numerous dose escalation methods exist with some used more commonly than others. According to Tourneau and colleagues, escalation methods are either 'rule-based designs' (RBD) including traditional 3+3 design and adaptations of this such as accelerated titration designs and pharmacologically guided dose escalation design; or, 'model-based designs' (MBD).[4]

Rule based designs

For studies of 3+3 design, three patients are enrolled to a cohort treated at the starting dose level[4]. The starting dose is guided by toxicological data from animal studies[4]. If none of the patients treated in a particular cohort suffer a dose-limiting toxicity (DLT), a further three-patient cohort is treated at the next pre-determined dose level. Should a patient experience a DLT, a further three patients will be enrolled at the same dose level. Typically, dose escalation will continue until at least two patients in a cohort of three to six patients experience a DLT. The definition of a DLT varies from trial-to-trial. Torneau et al. support this view and concluded that determining whether toxicity is dose limiting is most frequently based on severity, with other factors such as duration and reversibility frequently ignored.[4]

A major disadvantage associated with 3+3 design is that there are many escalation steps (dose levels), which cause a large number of patients to be treated at potentially sub-therapeutic doses.[4] In an attempt to reach the maximum tolerated dose quicker with fewer dose levels and to reduce the number of patients treated at potentially sub-therapeutic doses, accelerated titration designs (ATD) have been used. ATD are heterogeneous in nature, making a single definition challenging.

These designs usually have aspects of 3+3 design but vary in that cohorts usually consist of one patient until a DLT occurs, with this occurrence causing subsequent escalation to revert to 3+3 design.[4]

Model based designs

MBDs are those which use statistical modelling to produce a more precise dose-toxicity curve and predict subsequent dose levels.[4] Should patients enrolled to existing cohorts experience DLTs, future dose predictions are corrected to account for these. All four MBD trials identified in this review described using Bayesian overdose control (BOC). It has been suggested that MBD expose patients to high toxic doses and BOC aims to prevent this through additional safety measures.[4]

Summary of escalation methods used

As seen in Table 1, RBD were far more popular than MBD which were used by just four trails (6.3%) of trials. Of the RBD, 3+3 was nearly twice as common as accelerated titration designs.

Table 1: Summary of dose escalation methods used.

Dose escalation method	No. of trials	No. that permitted IPDE (%)
3+3	31	7 (22.6)
Modified 3+3[a]	3	0 (0)
ATD	16	4 (25)
Other accelerated designs[b]	4	1 (25)
MBD	4	1 (25)
Other[c]	6	0 (0)

a. Did not give detail of their modification, preventing further analysis
b. Varied substantially from a typical ATD but incorporated an accelerated design component
c. A lack of detail prohibited categorisation or the dose escalation design described did not align with a category

Intra-patient dose escalation

Intra-patient dose escalation (IPDE) is where individual patients are treated at more than one dose level; an additional measure to prevent many patients being treated at potentially sub-therapeutic doses. IPDE was used in 14 studies, whereas, 13 studies clearly stated that they did not allow this. The remaining 37 studies (57.8%) did not explicitly state whether they did or did not use IPDE. It was hypothesised that studies which enrolled fewer patients, primarily to save time, would be more likely to have permitted IPDE; however, analysis concluded the contrary. Studies which allowed IPDE enrolled an average of 47 patients vs. 33 for those which did not, a difference of 42%. This suggests that the primary reason for using IPDE may be to substantiate results rather than as a way of reducing the time spent enrolling a suitable number of patients to each dose level. Furthermore, as seen in Table 1, there was negligible difference in the use of IPDE between different escalation designs.

Blinding

In agreement with previous literature findings that oncology trials are predominantly open label[4], 63 of 64 PMD trials (98.4%) were open-label. One trial did not mention blinding.

Number of arms

In order to allow for a more meaningful inter-trial comparison, a standardised definition for trial arm has been used and applied to each trial: 'Where patients are treated differently in respect to anything other than a change in dosage strength'.

For example, if an infusion was given over 30 minutes to some patients, but over 3 hours to other patients, each group of patients has been classed as a distinct trial arm.

From applying this definition, 38 trials consisted of a single arm, 20 had two arms and six trials had three arms.

Dose levels of rule based designs: ATD vs. 3+3

In their published form, trials are difficult to compare with respect to their number of dose levels. Some authors simply list the different dose levels but do not detail whether, for some reason, levels have been used more than once (e.g. if toxicity occurs which causes a decrease to a previously used dose level), whilst others fully describe cohort progression including any repetition. For this reason, in order to enable a degree of comparison, this review has translated dose level information from each trial into unique dose levels (UDLs). This is where repeated dose levels have been removed giving a total number of 'unique' dose levels. Dose levels have also been ordered by magnitude to enable an analysis of dose increments. Figure 2 is an example of this translation for 'trial X'.

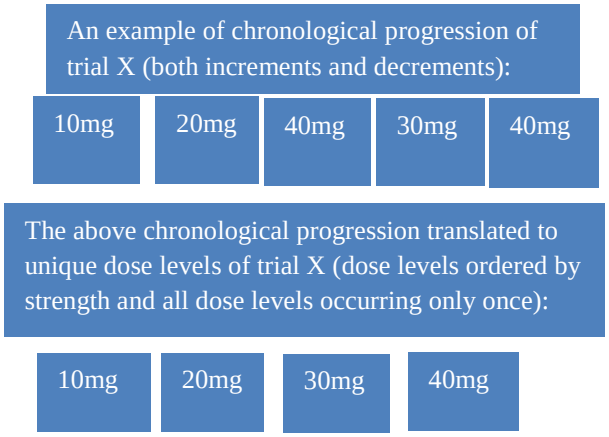

Figure 2: Trial X.

The mean number of UDLs used by ATD trials (n=16) is not significantly different from the mean number of UDLs used by trials of 3+3 design (n=31), (9.4 vs. 8.5; p-value=0.31). Figure 3 displays the distribution of the number of UDLs used for each ATD and trails of 3+3 trial reviewed, across all arms. The number of UDLs used by each of the 16 ATD trials had a range fairly evenly

distributed between 5 and 14 levels, except for five trials which used 10 UDLs. Trails of 3+3 design used a greater range of UDLs than ATD trials. Trials of this method also used different numbers of UDLs.

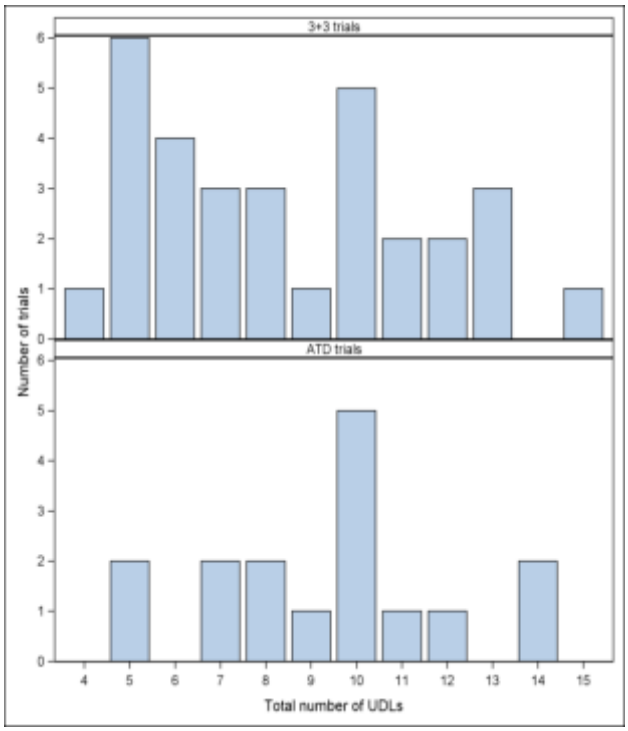

Figure 3: Dose level distribution for ATD and 3+3 trials.

It is difficult to draw significant conclusion from comparing the number of UDLs used in ATD and 3+3 trials because nearly twice as many 3+3 trials than ATD were reviewed (31 vs. 16). Furthermore, it may not be appropriate to compare trials that have a different number of arms.

Determining dose level increments for studies using rule based designs

Dose escalation designs are primarily concerned with cohort progression, DLTs and the MTD; however, determining dose increments is also of great importance. According to Torneau et al, incremental increase has been determined by use of a modified Fibonacci (MF) sequence, where dose increments become smaller as the dose increases[4]. Fourteen studies described how dose increments were determined. Of these, nine used MF, four switched to MF following an accelerated phase and one trial used pharmacokinetic data to guide dose increments but then switched to a MF technique.

All four studies which described switching to MF following an accelerated phase were of either 'accelerated

titration design' or 'other accelerated designs'. In general, these studies used 100% dose increments for a number of cohorts before switching to MF.

Dose level increments: ATD and 3+3

The authors sought to determine how dose level increments differed for trials of ATD and 3+3 design. Given the purpose of the ATD escalation method, it is expected that trials of this method would have larger dose increments than 3+3 trials in order to reach the MTD quicker and expose fewer patients to potentially sub-therapeutic doses.

However, to achieve this, it is necessary to know the chronology of dose levels used by the trials analysed so that each dose level can be compared to that immediately before it and a percentage increment determined via ((n+1)-(n))/(n)×100 (where n=dose level). In doing so, an appreciation of dose level changes over time could be gained. For example, if a trial had a second dose level of 50mg and a third dose level of 100mg, this would be ((100)-(50))/(50)×100=100% increment. But, this approach is not possible because, as aforementioned, trial publications vary in how they describe dose levels used and they also do not always describe whether the dose levels stated are chronological or not. For this reason, the previously described UDL approach as in Figure 2 has again been used.

Using Unique Dose Levels to investigate dose level increments

Using UDLs as a surrogate for chronological dose levels does not enable analysis of how trials truly progressed, for example, if a trial used the dose level Xmg three times at various points throughout its chronological progression, this is translated to one UDL of Xmg. Another way of describing the use of UDLs is that all trials have been 'standardised' to their optimum progression, this being an upward progression of 'unique' dose levels with any decrements (often due to toxicity), and subsequent repetition of dose levels due to said decrements, removed. As this translation has been applied to trials of both 3+3 and ATD escalation methods, comparison has been conducted.

In order to visualise the trials under investigation a graphical heat map method of analysis has been employed. Figure 4 is a heatmap displaying percentage increments (y axis) for trials of ATD and 3+3 escalation methods. Each map plot represents an individual percentage increment of an individual trial. The darker an area of the heatmap is, the more plots are represented. Each increment is categorized by the number of unique dose levels of the trial it originates from (x axis). Percentage increments have been calculated within each arm of a trial, rather than across arms. Figure 5 of 'trial Y' is an example of how individual heat map plots have been developed.

Learning from the heatmap

As previously discussed, comparison between trials of ATD and 3+3 design is limited due to the differences in the number of these trials reviewed (16 vs. 31). Despite this, and contrary to expectation, dose level increments for trials of ATD do not appear to be greater than those of 3+3 design. If this were the case, more ATD plots would be positioned near to or at the 100% line when compared with plots of 3+3 trials.

The heatmap is also useful in visualising the previous discussion that the number of UDLs used by ATD trials is not significantly different than those of 3+3 design. ATD plots to the left hand side of the heatmap are those with fewer UDLs; as can be seen, plots for trials of ATD design are no more plentiful in this region than those of 3+3 design.

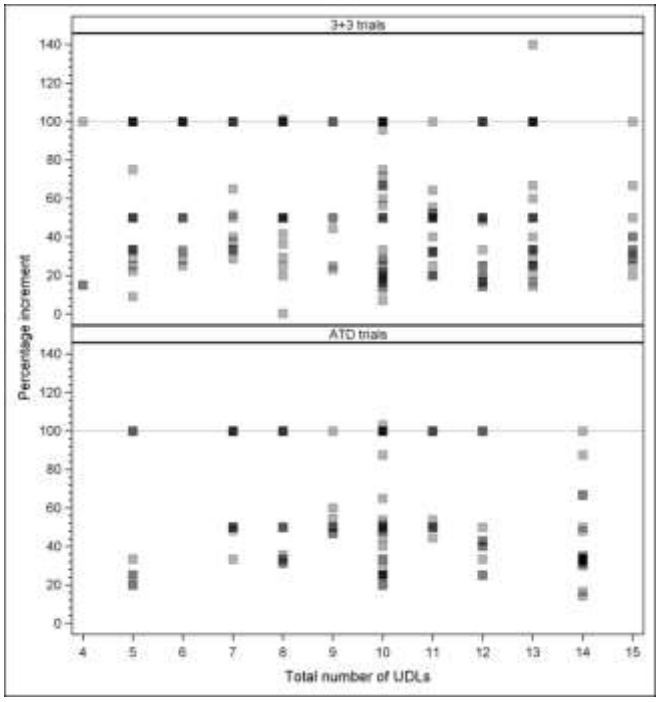

Figure 4: Heatmap of UDLs vs. percentage dose increment.

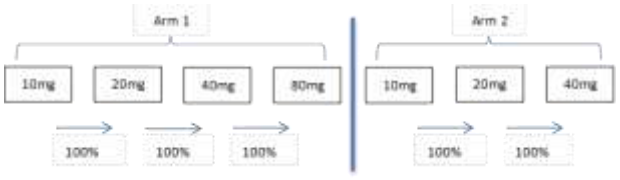

Figure 5: Trial Y, an ATD trial, would have five plots at 100% increment (y axis) and 7 unique dose levels (x axis) on the ATD heatmap.

Patient particulars

ECOG status

Trials enrolled an average of 44 patients. Forty-eight studies indicated their patients' performance status using the eastern co-operative oncology group (ECOG) grading system. The system is based on patient's ability to perform activities of daily living with a grade of zero being where patients are fully active and a grade of five being where patients are deceased. Of these 48 studies, 29 included patients distributed across three gradings while 19 included patients distributed across two. Definitions of ECOG grading's can be seen in Table 2.

Table 2: ECOG performance status.

Grade	ECOG performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Figure 6 details the ECOG status distribution of patients enrolled. An average of 36% of patients had a grade of zero, 54% had a grade of one and 10% had a grade of two (data rounded). No studies enrolled patients with an ECOG status >2.

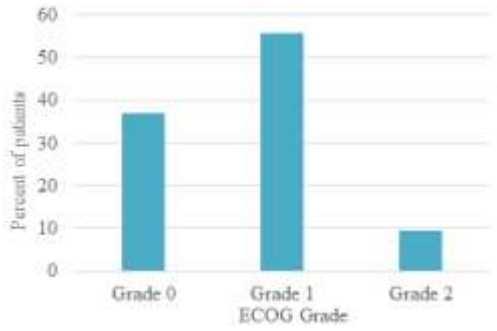

Figure 6: ECOG status of patients enrolled to all trials.

Primary diagnoses

Fifty-seven trials detailed the primary diagnoses of their patients. As seen in Figure 7, patients of certain diagnoses were more likely to be recruited into clinical trials than others. For example, 83% of trials enrolled patients with colorectal cancer versus 58% for lung cancer. Furthermore, the number of patients enrolled varied by diagnosis, e.g. when studies enrolled colorectal cancer patients, these patients constituted 23% of the trial population; however, for lung cancer this figure drops to 11%. The most striking example of this is with the diagnosis of leukaemia. Only two studies included patients with leukaemia, but of these studies, leukaemia patients constituted 67% of the trial population. This contrast is likely due to the pathophysiological differences between solid tumours and haematological cancers, e.g. trials of leukaemia candidates require leukaemia patients, whereas for solid tumours, the particular diagnosis may be less relevant.

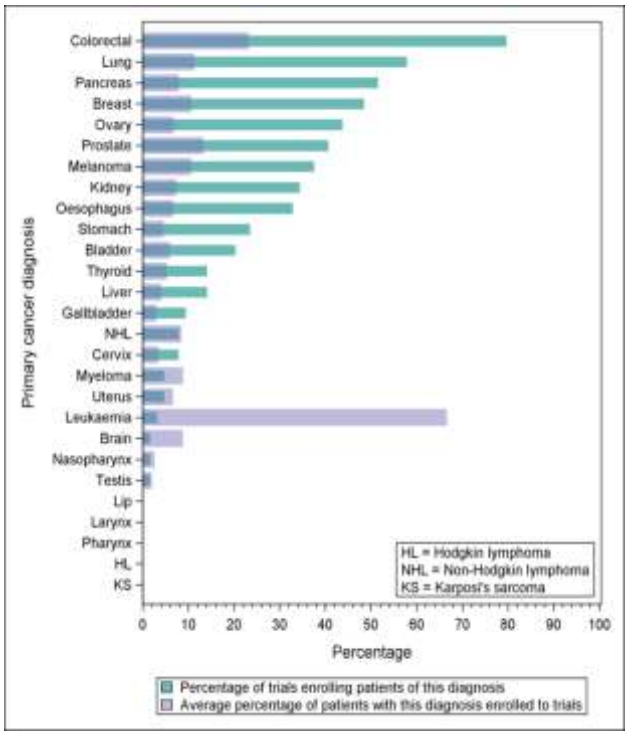

Figure 7: Enrolment popularity by primary diagnosis and, where enrolled, the average percentage of patients per trial.

On average, excluding the 'other' category, studies enrolled patients of six different cancer diagnoses. A previous review also found that patients enrolled to these trials have a broad range of diagnoses with over 80% having gastrointestinal, breast, gynaecologic, sarcoma or urologic cancers.[79]

Large variation in the diagnosis of patients enrolled suggests that the specific diagnosis of patients enrolled is not crucial at the FIH stage. This is reasonable given that the primary focus of FIH trials is to learn more about the safety profile of a drug candidate and define the MTD rather than investigate efficacy in patients of more specific disease characteristics, which is usually reserved for phase II trials.[79,80]

Drug administration and formulation

Administration route

All 64 PMD studies detailed a route of administration used to dose patients with 39 opting for enteral (PO) administration and the remaining 25 using intra-venous (IV) administration. Not all studies disclosed information regarding any particular formulation(s) used; for studies that did, the formulations used and their popularity can be seen in Table 3.

PO

It is well established, for marketed products, that PO administration is preferable over IV administration for numerous reasons such as reduced cost, reduced pain and reduced infection risk. It is likely that these reasons also partially explain an apparent preference for PO administration compared to IV in this review of FIH trials; but, given the time pressures of drug development, PO administration may also be preferred due to a quicker formulation process for oral dosage forms (particularly capsules).

IV

Twenty-four of 25 studies using IV administration published the length of time over which they infused patients. Infusion times ranged from 15 minutes to 3 hours. Two studies used two different infusion times, with patients of each falling within separate arms.

Table 3: Formulation popularity.

	Formulation used	No. of trials
PO	Capsule	17
	Capsule and liquid	1
	Capsule and powder	1
	Tablet	6
	Tablet and liquid	3
	Unknown	11
IV	Infusion	25

Dosage form and trial design

Interestingly, 19/31 (61%) of trials of 3+3 design reviewed used PO administration whilst only 12/31 (39%) used IV administration. When compared to trials of accelerated titration design (ATD), these values are 7/16 (44%) and 9/16 (56%) for PO and IV respectively. This suggests that trials of 3+3 design are more likely to use PO administration and ATD trials are more likely to use IV administration. In order to determine whether these relationships are causal or casual, additional variables would need to be extracted from trial publications and a multivariate analysis completed.

Route of administration and number of arms

A comparison of the number of arms used with IV and PO routes of administration indicates that trials with more arms are more likely to use PO dosage forms. As seen in Table 4, the vast majority (80%) of trials using IV administration only had one arm, with no trials having three arms. However, trials using PO administration consisted of one, two or three arms with a sizeable proportion (38.5%) having two arms, 18.5% more than those using IV administration.

Table 4: A comparison of the number of arms per trial grouped by route of administration.

Route	No. of trials with 1 arm (%)	No. of trials with 2 arms (%)	No. of trials with 3 arms (%)	Total
IV	20(80)	5(20)	0(0)	25
PO	18(46.2)	15(38.5)	6(15.4)	39
All	38(59.4)	20(31.3)	6(9.4)	64

In addition to the reasons previously discussed regarding a general preference for PO administration, there are numerous reasons as to why PO administration may be preferable to IV administration for studies with a greater number of arms. One reason could be that PO administration offers increased flexibility for trials with a large range of dose levels; infusions may be limited to a certain drug concentration for administration which is further limited by maximum amounts of diluent that patients can receive.

Route of administration and number of patients

Given the challenges of IV administration when compared to PO administration, we sought to determine whether trials with a greater number of enrolled patients would be more likely to use PO administration. A comparison of the number of patients enrolled to IV and PO trials (42 vs. 45; p-value=0.57) concludes no significant difference.

Parallel single dose trials

Five PSD trials were identified and reviewed, one phase 0 trial which enrolled patients and four phase 1 trials which enrolled volunteers. One of these trials had aspects of both PSD and PMD trials, but as it was predominantly PSD in nature, only its PSD aspects have been reviewed. Given the small number of PSD trials identified and reviewed, descriptions rather than analyses of the data have been included:

- Like PMD trials, the majority (3/5) had their corresponding author located in the United States
- PSD studies were more likely to be publicly funded than PMD studies (40% vs.7%)

- These trials had between three and seven dose levels, with a mean of five
- Three of the volunteer studies described dosing some participants with placebo, with the most common active:placebo ratio being 3:1
- Three volunteer studies used double blinding, with a single volunteer study and the patient study being open label. All trials administered their investigational drug orally, with two describing using tablets and one using capsules.

Limitations

A number of limitations have been identified throughout this study. Firstly, the content of trial publications varied which produced an incomplete dataset for certain discrete variables. Some variables were affected more than others e.g. IPDE for which 37 studies did not detail whether they did or did not use IPDE.

Secondly, authors define trial terminology differently which makes data extraction and analysis more challenging e.g. trial arm. This is to be expected given the global scale of research. In order to overcome this, where appropriate, standardised definitions need to be produced and applied to all trials to ensure consistency and validity of conclusions made. In this review, a definition of trial arm was produced to enable comparison: 'where patients are treated differently in respect to anything other than a change in dosage strength'.

Summary

This review has been extensive in investigating how 69 FIH oncology trials of small molecules vary with respect to the four areas previously described. For trial design, the escalation methods of first-in-human oncology trials vary with ATD and 3+3 being most common. Unexpectedly, the numbers of dose levels used by these methods do not differ significantly and the dose level increments of these methods are similar. Those enrolled to FIH oncology trials vary in both diagnosis and status. Patients with colorectal cancer are most likely to be enrolled and patients are more likely to be administered an investigational drug PO rather than IV.

The impact of FIH trial variation on cancer research outcomes has not been determined throughout this review. It is likely that certain variation has a greater impact. For example, with respect to trial design, the ATD approach may not identify a maximum tolerated dose speedier than 3+3 trials which has clear research cost implications. Further research should be undertaken to investigate the impact of the variation identified on cancer drug research and development.

Clear differences in the content of trial publications made a collective review challenging. Given that the content of published trials is inconsistent, standardised publication criteria may be beneficial for the investigation of clinical trials and their impact on the development of evidence-based oncology medicines. In a world where the prevalence of cancer is expected to increase over the coming decades, such medicines are needed to provide patients with effective treatments.

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