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EXPERT OPINION

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How can attrition rates be reduced in cancer drug discovery?

Lucas Moreno[†] & Andrew DJ Pearson
[†]*Paediatric Drug Development, Children and Young People's Unit, The Royal Marsden NHS Foundation Trust, Sutton, UK*

Attrition is a major issue in anticancer drug development with up to 95% of drugs tested in Phase I trials not reaching a marketing authorisation making the drug development process enormously costly and inefficient. It is essential that this problem is addressed throughout the whole drug development process to improve efficiency which will ultimately result in increased patient benefit with more profitable drugs. The approach to reduce cancer drug attrition rates must be based on three pillars. The first of these is that there is a need for new pre-clinical models which can act as better predictors of success in clinical trials. Furthermore, clinical trials driven by tumour biology with the incorporation of predictive and pharmacodynamic biomarkers would be beneficial in drug development. Finally, there is a need for increased collaboration to combine the unique strengths between industry, academia and regulators to ensure that the needs of all stakeholders are met.

Keywords: anticancer drug development, attrition rate, biomarkers, drug discovery

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1. Introduction

Over the past decade, a large number of novel anticancer drugs have been developed and many are now implemented into routine clinical practice [1]. Some of these drugs have made improvements in overall survival for all patients with a given condition, whereas others have only shown benefit in smaller groups of patients with known molecular aberrations.

However, the development of new anticancer drugs remains an expensive and inefficient process. In anticancer drug development, attrition rate is the major factor that reflects the level of loss of new candidate drugs during the process from pre-clinical to clinical and through their clinical development. Less than 5% of drugs that reach Phase I gain a marketing authorisation (MA) [2]. Even more, it has been reported that only 1 in 10,000 pre-clinical compounds ever reach the market [3].

It is envisioned that a more scientific and biology-driven drug development practice would lead to more efficiency, but to date this has only been successful for relatively small populations with known molecular aberrations by using predictive biomarkers in the development of such potent inhibitors. Giving drugs that match key genomic aberrations in the patients promise to produce a much greater benefit in smaller patient populations [4]. This has been defined as the 'inverted pyramid' paradigm, where for drugs developed classically a large population is required to achieve a small benefit (the standard pyramid). Using agents targeted against specific molecular aberrations, a small population is targeted but the benefit obtained is large (the inverted pyramid).

Numerous solutions have been proposed to tackle the issue of attrition in anticancer drug development by many authors [5-11], which has even been defined by some as 'The Valley of Death in anticancer drug development' [12]. Reported factors are innumerable and include scientific and financial or non-scientific

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reasons. The latter might include lack of resources, wrong incentives, aggressive pricing strategies or adverse regulatory environment, while the scientific reasons include considering tumour microenvironment, cross-talk and negative feedback loops, development of resistance, exposure time, drug delivery or the choice of pre-clinical models. While many of these issues have been reviewed elsewhere extensively, this editorial assesses and comments on the most relevant and promising scientific strategies to improve attrition rates in the development of anticancer drugs in the authors' opinion.

2. Better pre-clinical drug development

Ideally, robust pre-clinical studies should identify the best drugs with the highest likelihood of efficacy and the least possible toxicity before starting clinical trials. There are major areas where improvements in pre-clinical testing would lead to more efficient drug development: first, a better identification and qualification of the targets that are of relevance to each tumour type is essential. Despite the difficulties related to the biological heterogeneity of cancers, some efforts have been made to achieve a consensus on the required data to pursue a set target both in adults and paediatric patients [13].

Second, better pre-clinical models more representative of human tumour biology need to be pursued. While pre-clinical studies in cell lines and xenografts are a useful tool to screen compounds and might provide useful early signs of interest, they have not shown good correlation with efficacy in Phase II trials or survival advantage in Phase III trials [14].

Although their final ability to predict success is still unproven, new models will better recapitulate tumour biology and microenvironment than multiple passaged cell lines or cell line-derived xenografts [15].

Robust examples of genetically engineered murine models (GEMM) are: KRAS-driven models of pancreatic cancer; MYC/MYCN-driven models of lymphomas/neuroblastoma or sonic hedgehog-driven models of medulloblastoma [16-18]. But recently also patient-derived cell lines and patient-derived xenografts are paving the way for a true personalised medicine approach [19].

While pre-clinical testing packages have significantly improved, evaluation of potential mechanisms of resistance is generally lacking. The development of feedback loops, new mutations, drug resistance or blockade of drug uptake should be incorporated in the evaluation of new therapies [20-24]. For example, a resistant smoothened mutation developed on a patient with medulloblastoma shortly after very successful treatment with a sonic hedgehog inhibitor [21,22]. It has been shown how the addition of MEK inhibitors overcomes the resistance to single-agent BRAF inhibition for BRAF-mutated melanomas [23-25].

In the clinic, anticancer agents are mostly given in combination schedules. The issue of combinations should be addressed in pre-clinical studies upfront in order to rationally design and guide clinical trials [26,27]. Finally, better pre-clinical models to assess toxicity or test different formulations are also needed. Too many drugs that go into Phase I/II clinical trials still have excessive toxicity or formulation problems that preclude further clinical development of potent inhibitors.

It is envisioned that a better selection of the drugs that reach Phase I trials with more stringent criteria to qualify targets, show antitumour activity or tolerability and develop formulations would reduce the number of failures during early clinical trials. Careful studies need to be established to relate efficacy in pre-clinical models with efficacy in Phase II trials.

3. Incorporation of biomarkers

Predictive biomarkers that select patients who are most likely to benefit from a targeted therapy based on the patient's molecular characteristics have already been shown to reduce attrition. Only 5% of drugs without patient selection reach registration as opposed to 47% of selected kinase inhibitors targeting specific patient genomic aberrations [4,28]. For these agents, response rates in Phase I/II clinical trials were above 50%, while 10% has been reported as the average response rate for Phase I trials without patient selection [4]. Nevertheless, it is important to note that premature decisions on biomarkers that have not been adequately validated and qualified might mislead the development of molecularly targeted agents [29].

More importantly, not all drugs and targets may have a simple ideal predictive biomarker. There will still be many drugs that make modest contributions to improving outcome that are valid when agents are combined into multimodal regimens for which there will not be a validated predictive biomarker [30]. For some conditions or targets mRNA signatures might provide better prediction than other genomic aberrations [31]. Where no predictive biomarker is still identified, collection of biological material and pilot analyses of tertiary biomarker end points is highly recommendable in order to identify novel biomarkers of response.

The issue of tissue heterogeneity remains unsolved. Differences between primary tumour and metastases [32] or circulating tumour cells [33,34] have been described and recently deep sequencing analyses have shown significant differences between regions of the same tumour [35] including the detection of good and poor prognosis signatures within the same tumour mass.

But as a result of the interest in predictive biomarkers, indications with known molecular aberrations might become overcrowded and competitive whereas fewer drugs are developed for most common heterogeneous cancers.

Similar to the pre-clinical setting, it would appear essential to avoid taking forward drugs that do not achieve the necessary target inhibition or downstream pharmacodynamic (PD) effects. The use of PD biomarkers provides the proof of principle of target modulation and should be a requirement

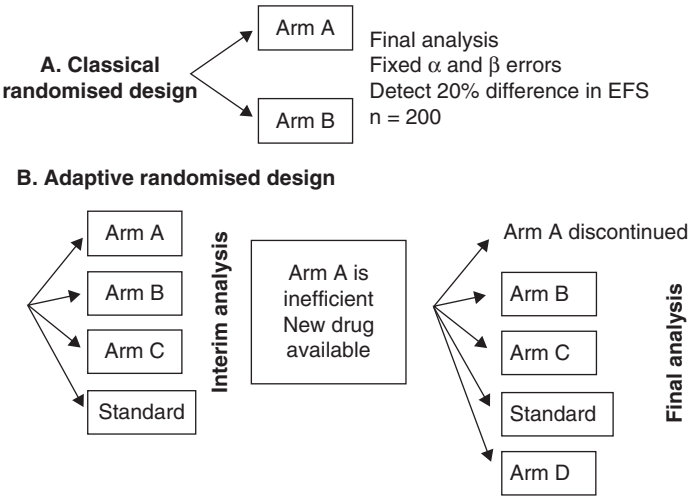

Figure 1. Differences between classic and adaptive randomised clinical trial designs.

prior to embarking on larger Phase II trials, following the 'Pharmacologic Audit Trail', a concept proposed by Workman and collaborators [36]. But, it still remains crucial to qualify biomarkers appropriately [29].

Phase 0 trials have been proposed by some authors as a bridge between pre-clinical and clinical drug development to accelerate and improve the efficiency of this process. The primary objective of these trials is to obtain pilot proof-of-mechanism/pharmacokinetic data at non-therapeutic drug exposures (e.g., by giving a single dose of a new investigational agent) in a small subset of patients, therefore identifying those drugs that do not achieve expected biological effects that would then be de-prioritised without further trials. A significant number of such clinical trials have been conducted to date, with some successful examples, such as the PARP (poly-ADP ribose polymerase) inhibitor ABT-888 [37]. However, ethical concerns about the complete lack of benefit and the repeated tumour biopsies involved are not resolved. Proving target inhibition with a single dose of a single drug might not be a good model to mimic the clinical setting, when sustained inhibition is required to maintain benefit from the agents or they have to be given in combination schedules to prevent the development of resistance [12,38,39].

Most PD biomarker studies require repeated tumour biopsies thus increasing the burden to the patients. It is therefore crucial to make the most rationale and efficient use of tumour material. A recent publication has shown how less than half of early clinical trials collecting PD analyses include that data in the final manuscript [40,41]. In many cases, surrogate biomarkers can be used to avoid sampling primary tumours [42].

It is essential that the selection of agents to take forward into early clinical trials is based on the availability of predictive and PD biomarker data which are developed pre-clinically and implemented into early clinical trials.

4. Efficient transition from early to late phase clinical trials

The decision to progress a drug from early Phase I/II/proof-of-concept clinical trials into randomised Phase III trials for the purpose of registration is extremely difficult, complex and costly. Companies have to consider not only scientific rationale but also the financial investment required, the available market and/or the anticipated returns more commonly referred to as the benefit to risk ratio [3]. This commits the company to continue the development of the agent(s) over the next quinquennium with the clinical trials enrolling hundreds if not thousands of patients. Hypothesis-driven biomarker-rich studies will importantly smoothen the progress of these decisions.

A number of innovative designs now facilitate the maximising of the information obtained from early clinical trials. Increasingly, Phase I trials include expansion cohorts at the recommended Phase II dose (RP2D) that target the population of interest in the search for early signals of activity. Well-designed Phase I trials incorporating tumour biology, predictive and PD biomarkers surely promise to detect ineffective or toxic drugs that should not progress further.

Randomised Phase II trials can provide more robust activity and efficacy data before proceeding to larger Phase III trials compared with single arm Phase II trials with historic controls [43]. Novel adaptive designs or Bayesian statistics allow randomised comparisons with smaller numbers of patients [44,45]. Some designs will allow testing several drugs, doses or combinations more efficiently: first, in a *pick-a-winner* design drugs are tested in several stages: in the first of which, patients are randomised between a number of different novel treatments and a control arm. Only those drugs that show a pre-specified degree of benefit at the end

of the first stage will proceed to the next stage(s). This allows testing a number of novel strategies in a randomised fashion without the limitation of conducting several larger-scale Phase III trials [46]. Second, *drop-the-loser* designs were developed to monitor multiple doses of an experimental treatment compared with a control arm before proceeding to a large randomised Phase III trial [47,48]. **Figure 1** depicts the differences between classic Phase II trial designs and novel adaptive designs.

In summary, novel designs will provide an efficient way of identifying 'winners' or dropping 'losers' in trials with a small number of patients. Where possible, all decisions should be evidence-based using information gathered from randomised trials, even in the Phase II setting with reduced numbers and more flexible power calculations.

5. Collaboration: industry, academia, regulators

Fundamentally all stakeholders involved in the development of anticancer drugs: industry, academia, regulators, patient advocates and policymakers must work together. The authors strongly believe that close collaboration will improve the efficiency of the drug development process and reduce attrition.

Academic partnerships, designation of orphan drugs, elaboration of Paediatric Investigational Plans (PIPs) are strategies that increase the revenues or decrease the costs of developing agents, therefore ensuring that drugs are profitable [49].

Regulatory bodies are now increasingly offering collaboration at multiple levels, and they provide scientific and regulatory advice that ensures that good and safe drugs are ultimately delivered to patients [50].

Additionally, academic partnerships can help provide access to larger cohorts of patients and thus bring new drugs forward into frontline treatment that would benefit the wider population of patients with cancer.

6. Expert opinion

Attrition is a significant and costly problem for anticancer drug development and must be addressed at all levels and stages of the drug development process.

Pre-clinically, better models are needed that will be more predictive of success in clinical trials and these need to be scientifically evaluated. GEMMs and patient-derived xenografts better recapitulate the patient's tumour biology. More efforts in drug discovery units will lead to less toxic, better formulated drugs and predictive biomarkers selecting patients with known molecular aberrations for specific kinase inhibitors have already been shown to reduce attrition, but are not applicable to all cancers.

PD biomarkers help in the go–no go decisions at the end of Phase I and ensure that new drugs modulate the target(s) as expected.

The decisions to take forward drugs from Phase I/II (proof-of-concept) to large Phase III randomised trials have to be taken carefully. Innovative trial designs such as RP2D expansion cohorts in biomarker-driven Phase I trials and randomised Phase II trials provide better information. These decisions must be based on robust scientific data and advice should be sought from academia and regulators alike.

Declaration of interest

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Affiliation

Lucas Moreno[†1,2] & Andrew DJ Pearson[1,2]
[†]Author for correspondence
[1]Paediatric Drug Development, Children and Young People's Unit, The Royal Marsden NHS Foundation Trust, Downs Road, Sutton SM2 5PT, UK
Tel: +44 0 208 661 3678;
Fax: +44 0 208 661 3617;
E-mail: lucas.moreno@icr.ac.uk
[2]The Institute of Cancer Research, Divisions of Clinical Studies and Cancer Therapeutics, Sutton, UK