Selecting the Best Drugs for Phase I Clinical Development and Beyond

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OVERVIEW

Attrition rates of drugs from human entry to regulatory approval are far higher in anticancer drugs than those for nononcology indications. In the era of molecular therapeutics that results from a deeper understanding in cancer biology and advancing technologies, the number of compounds available for clinical testing is likely to continue to increase. Although the main objectives of phase I trials are to characterize toxicities of new agents and to determine the recommended dose for phase II development, most phase I studies are now designed to provide some early signal on preliminary efficacy as secondary objectives. The “go-no-go” decision to further develop a drug, or not, is now often pushed forward to the phase I setting. Thus, there is a need for investigators to be able to critically review the preclinical data available in order to determine which drugs should advance on the developmental path. This review highlights the intrinsic characteristics of a drug and the relevant data to be collected during its preclinical assessment, which may maximize the chances of success in clinical testing and eventual regulatory approval.

Novel treatments for cancer are tested initially in phase I trials, enrolling patients with advanced disease who have exhausted or lack standard treatment options. Although these trials are designed to evaluate safety and to define dosing for future efficacy trials, most patients volunteer with the hope of obtaining personal medical benefit. Traditionally, it has been quoted that only 5% of agents identified as potential anticancer compounds entering human testing demonstrated sufficient clinical activity in phase III trials to be eventually licensed for clinical use. This is significantly lower than the success rate of 20% noted for drugs used in cardiovascular disease. However, the reported attrition rate of oncology drugs has been variable. A recent analysis of over 970 anticancer agents which entered clinical development between 1995 and 2007 has shown an attrition rate of 82%, suggesting that roughly 1 in 5 drugs tested in phase I trials achieved registration. For kinase inhibitors, the phase transition probability values were even higher, with an overall attrition rate from phase I to registration of only 53%. This same analysis also showed that the transition from phase II to phase III is the step with the highest risk involved in the clinical development pathway. Despite the variability of these reports, patient and clinical trial resources to support drug development are limited. As such, strategies to minimize attrition and shorten the timeline from human entry to registration are urgently needed.

In the era of molecularly targeted therapeutics, “go-no-go” decisions are often made earlier on in the developmental process than during the phase II to III interface. A deeper understanding of the biologic networks and pathways implicated in the pathogenesis of cancer has uncovered many druggable targets. Furthermore, advances in techniques used in preclinical testing have led to an ever-increasing number of compounds suitable for clinical investigations. Despite a rapid expansion of available drug candidates for early phase testing, failures remain prevalent in the clinic as a result of many potential factors. These may include inadequate preclinical evaluations before lead candidate selection for human entry, unacceptable therapeutic index for clinical development, or pharmacokinetic liabilities, among others. Given the high costs associated with the conduct of later phase trials, especially randomized phase II or III trials, many companies discontinue development of their compounds if they cannot establish proof-of-mechanism by the end of phase I testing. Thus, aside from assessing toxicity and tolerability, many phase I trials have now assumed an additional role as “gate-keepers” in drug development. This article aims to identify characteristics in the preclinical development of a candidate drug which have been associated with success in the later stages of clinical investigations. It will also explore ways to improve the robustness of data collected from phase I trials, thus enabling steadfast go-no-go decisions to be made.

GETTING DRUG DEVELOPMENT RIGHT UNDER THE CURRENT FRAMEWORK

Robustness of Preclinical Data

Ideally, preclinical investigations of candidate drugs should provide information about the mechanism of action of the
drug, identify pharmacodynamics markers of activity, clarify toxicity profile, and identify mechanism of resistance and how to overcome them. Data derived should have face validity scientifically and, preferably, similar results should be reproducible in multiple models and be corroborated by other sources. One of the challenges in anticancer drug development lies in the erroneous use and misinterpretation of preclinical data from cell lines and animal models. Preclinical studies of candidate drugs which ultimately fell-by-the-wayside during the later phases of development often only included small numbers of poorly characterized tumor cell lines that inadequately recapitulate human disease. Serially passaged, immortalized cell lines often lose their molecular complexities and are subjected to cross contamination, therefore are not reflective of the behavior of advanced solid tumors. Furthermore, in vitro models cannot reliably assess the tumor microenvironment, which may exert relevant anticancer effects in many neoplasms.

The type of preclinical models used has an important bearing on the robustness of available data. Generally speaking, in vivo models are more informative than in vitro models, especially those that are not simply derived from commercial cell lines. Genetically engineered mouse models (GEMM), in which the expression of a protein is temporally and/or spatially controlled by genetic manipulation, can better assess transformation events and potential anticancer activity related to the inhibition of a particular protein or pathway.

Benefits of GEMM for preclinical evaluation include that the tumor was developed in an immune-competent animal and genetic alterations can be modified both in a time- and tissue-specific manner. Although this is more characteristic than either patient-derived or passaged cell line xenograft models, molecular alterations in GEMM are limited to the ones that have been introduced, whereas in reality there are often multiple abnormalities in human cancers.

Patient-derived tumor xenografts (PDTX) is another reliable model to predict clinical activity of novel compounds in cancer treatment. This is performed by directly engrafting surgically resected tumor samples into immuno-compromised mice. Advantages of this technique over standard cell line xenograft models include its ability to maintain the molecular, genetic, and histologic heterogeneity typical of tumors of origin through serial passaging in mice. Detailed molecular profiling of PDTX can now be performed such that single agents or drug combinations can be tested in models not only defined by histology, but also by their molecular aberrations. Well-characterized PDTX can also potentially reduce noninformative animal studies while providing a more relevant system to test clinically directed hypotheses.

**Preclinical and Clinical Evaluations of Pharmacodynamic Biomarkers**

Biomarkers, whether pharmacodynamic or predictive, identified in preclinical studies form an important bridge in the translation to clinical investigations. Once the target and mechanism of antitumor activity have been evaluated by using in vitro models, experiments should be undertaken to ensure that target inhibition can be achieved at tolerable doses in vivo. Pharmacodynamic biomarkers provide proof-of-mechanism while predictive biomarkers help distinguish responders from nonresponders. Rigorous assessment of pharmacodynamic and predictive biomarkers in robust preclinical models can yield promising results that help guide correlative studies planning and patient selection in early phase trials. An example of an informative preclinical repository is the Cancer Cell Line Encyclopedia (CCLE) project (www.broadinstitute.org/ccle/home), which is a compilation of gene expression, chromosome copy number, and massively parallel sequencing data for 947 human cancer cell lines. As an online collaboration between academia and the pharmaceutical industry that is openly accessible by the public, it has the potential to enable comprehensive predictive modeling of drug sensitivity and resistance.

The inclusion of biomarkers in phase I trials has increased over time; 14% of phase I studies submitted as ASCO abstracts in 1991 included correlative studies with biomarkers compared with 24% in 2002 (p < 0.02). This trend is almost certainly continuing to rise. Fresh tumor biopsies are often requested serially pre- and post-treatment for correlative studies. Improvements in functional imaging have also allowed more in-depth assessment of pharmacodynamic changes. Examples of pharmacodynamic biomarkers may include variables measured at multiple time points, such as...
immunohistochemical expression of an activated protein in tumor tissue before initiation of and during treatment.\textsuperscript{15} Others may include serial measurements such as changes in serum concentrations of growth factor, or changes in standardized uptake values of target lesions on fluorodeoxyglucose positron emission tomography scans before and after drug administration. Dynamic contrast enhanced magnetic resonance imaging has also allowed visualization of vascular distribution and blood flow which can be used to monitor antiangiogenic agents. Early readouts of a pharmacodynamics biomarker can serve as a predictive biomarker, if the changes are reflective of biologic activity in the tumor. Other examples of predictive biomarkers include mutational or amplification status of a gene that is determined to be a driver of the disease under investigation.

**Favorable Characteristics for a Drug to Enter First-in-Human Testing**

Specific characteristics of a drug and its molecular target(s) should be considered in the prioritization of anticancer compounds for clinical development. In cases in which compelling preclinical data exist which readily distinguish sensitive from resistance populations, an upfront enrichment strategy as early as in phase I trials may be justified to facilitate patient selection. Examples of such unique agents include vemurafenib for patients with melanoma which harbor \textit{BRAF V600E} mutations\textsuperscript{16} and crizotinib for patients with non-small cell lung cancer with \textit{EML4-ALK} translocation.\textsuperscript{17} First-in-class compounds with novel molecular targets deemed scientifically critical to tumor growth and progression should also be given priority, as they may shed insight into previously unknown or uncertain oncogenic pathways. Most drug developers discourage the development of “me-too” agents unless there are distinctive advantages over existent drugs. These advantages may include a superior therapeutic index, enhanced pharmacokinetic profile, or improved target specificity, among others. Table 1 illustrates some examples of recent drugs with these favorable characteristics that led to their prioritization in clinical evaluation.

**Preliminary Investigations with a Phase 0 Trial**

Recommended by US Food and Drug Administration (FDA) guidance in 2006, the phase 0 trial is a new type of first-in-human study conducted to assess drug effects on a molecular target, by means of a pharmacodynamic assay in a small number (10–15) of patients.\textsuperscript{18–21} In phase 0 studies, micro-doses or limited doses of a drug are given to patients to confirm the expected pharmacokinetic and pharmacodynamic properties in humans. Patients in these studies enroll purely for altruistic purposes as the limited treatment doses or duration of these studies preclude any potential for a meaningful treatment response. Human data collected from phase 0 trials can be used to optimize the design and conduct of subsequent phase I trials, as preclinical testing in unreliable models can often be misleading. Phase 0 studies can be conducted before the completion of toxicology studies required for the investigational new drug application. They can also be used to prioritize among analogs or agents designed to interrogate the same molecular target by the comparisons of pharmacokinetic or pharmacodynamic characteristics, or via imaging studies for localization of the agent to the tumor.\textsuperscript{15} Although a phase 0 trial can by no means replace a phase I trial, it can include several escalating dose levels, the results of which can help define the appropriate dose range and administration schedule to take into phase I testing. Likewise, phase 0 trials, with their pharmacodynamic endpoints, will not eliminate the need for phase II trials to establish the agent’s ability to yield tumor response or clinical benefit. They may, however, advocate for early termination of development of agents that fail to yield the anticipated biologic effect.

**Quality Design and Execution of the Phase I Trial**

A well-designed and executed phase I trial is essential for investigators to take a drug to the next level of development. Recently, many phase I trials have been conducted not only with the aim to establish a safe and reliable recommended dose and schedule for phase II development, but also to provide a head start on the identification of specific target populations.

The reporting of data needs to be complete with rational justification for the activities and toxicities seen. Drugs which demonstrate favorable pharmacokinetic profiles in phase I trials, such as those with dose linearity and attainment of biologically relevant concentrations in preclinical models, are more likely to be successful when brought to further stages of drug development.

In traditional phase I trial designs, dose-limiting toxicities are commonly defined within the first cycle of treatment. This approach has been acceptable with conventional cytotoxics when treatment is only given for a short period in the beginning of every cycle, followed by a rest period, over a predefined number of treatment cycles. Unlike conventional cytotoxics, the administration of molecularly targeted agents is likely to be chronic and prolonged until disease progression or evidence of resistance. With sustained drug exposure, delayed or cumulative severe toxicities beyond the first treatment cycle are relevant and should be considered in the dose recommendation process. Similarly, moderate toxicities, which may be bearable for a short period of time,
may be considered intolerable when experienced chronically. A retrospective review of over 440 consecutive patients recruited into phase I trials of molecularly targeted agents in two large European cancer centers between January 2005 and July 2008 showed that 50% of patients had their worst grade toxicities after cycle 1 of treatment, with the risks of grade 3 and 4 toxicities up to 3% in the first 6 cycles of treatment.22 This finding supports the rationale to incorporate toxicities experienced beyond the first cycle in the determination of the recommended phase II dose.

**Source of the Investigational Drug**

To effectively and efficiently evaluate a drug from bench to bedside requires experienced hands and a well-oiled infrastructure. The need to seek regulatory approvals in various stages of preclinical and clinical development stipulates the familiarity with good practice guidance and the presence of well-tested standard operating procedures. Although such practices and processes are often already in place in larger and more established pharmaceutical companies, this does not infer that small pharmaceutical or biotechnology companies are any less reliable or experienced in early phase drug development. Rigor in maintaining quality control and quality assurance, exerted by both pharmaceutical companies and academic investigators, is crucial to ensure reliability and integrity of any data generated.

**Relationship between Preclinical Investigators, Sponsors, and Clinical Investigators**

The preclinical investigations of a drug form the foundation on which the pillars of further development and hopefully subsequent approval rest. The quality of the science that has been generated and reported during this initial phase needs to be held to an extremely high standard to ensure robustness and validity of the results. Preclinical investigators are often either independent academics or employees of large pharmaceutical companies, which may also be sponsors in subsequent studies of the same compound. Regardless of the source, it is essential that the data generated are accurate and scientific ethics upheld. Additional credit should be given to studies of which results have been readily reproduced, either independent academics or employees of large pharmaceutical companies, which may also be sponsors in subsequent studies of the same compound. Regardless of the source, it is essential that the data generated are accurate and scientific ethics upheld. Additional credit should be given to studies of which results have been readily reproduced, either by peers in the scientific community or by the investigators themselves.

An open and honest exchange of ideas between the pharmaceutical sponsors and the investigators in the planning, design, and execution of the phase I trial are vital to ensure success. There should be a feedback mechanism readily in place from the investigator to the sponsor while the trial is underway to resolve any potential problems that were not anticipated during the planning period. Investigators should not be reluctant to share views that are relevant but may not necessarily be desirable for the development of the drug—such candid dialogues are important to ensure that the drug is being developed with solid fundamentals.

**THE NEXT STEP FORWARD: RECOMMENDATIONS FOR IMPROVING THE RELIABILITY OF PRECLINICAL STUDIES**

Cancer research is constantly evolving. As new targets are sought, signaling pathways are elucidated, and drugs are developed, the methodology and framework for drug discovery and testing also need to evolve. The complexities associated with experimental therapeutics require that clear steps be taken to ensure robustness of preclinical investigations.

The traditional divide between preclinical and clinical investigators needs to be broken. Both groups will benefit from better communication with patients. Data from prior studies should be made readily available to other investigators. Although positive data need to be made available for peers to review and reproduce to ensure their robustness, there also should be opportunities and venues for investigators to share negative data in conferences and publications. The establishment of clinical trial registries administered by public bodies, such as Clinicaltrials.gov by the US National Institutes of Health, has ensured that the status of ongoing trials can be followed. It also provides a platform for the investigators to post their results—including negative ones. Negative data should be considered just as informative as positive ones. Negatives data need to be made available for peers to review and reproduce to ensure their robustness, there also should be opportunities and venues for investigators to share negative data in conferences and publications. The establishment of clinical trial registries administered by public bodies, such as Clinicaltrials.gov by the US National Institutes of Health, has ensured that the status of ongoing trials can be followed. It also provides a platform for the investigators to post their results—including negative ones. Negative data should be considered just as informative as positive ones. Negative data should be considered just as informative as positive ones.

**CONCLUSION**

There have been great advances in cancer drug development over the past two decades. As a result of the rapid increase in

**TABLE 2. Decision Process on Whether to Bring a Drug Forward for Further Development after Completion of the Phase I Trial Based on Early Clinical Efficacy Signals and Pharmacodynamics Biomarker Results**

<table>
<thead>
<tr>
<th>If the phase I trial showed:</th>
<th>Clinical Activity</th>
<th>No Clinical Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD Activity</td>
<td>GO</td>
<td>GO versus No-GO depends on:</td>
</tr>
<tr>
<td></td>
<td>GO</td>
<td>● Robustness of clinical and PD data that declared its lack of activity</td>
</tr>
<tr>
<td></td>
<td>GO</td>
<td>● Validity of PD assays</td>
</tr>
<tr>
<td></td>
<td>GO</td>
<td>● Priority among other agents in the drug development pipeline and competitive landscape</td>
</tr>
</tbody>
</table>

No PD Activity ● But need to re-evaluate the mechanism of action of the drug and also assess the validity of the PD data

No:GO

Abbreviation: PD, pharmacodynamics.
number of compounds available for testing and better understanding of molecular cancer biology, phase I clinical trials now tend to play other roles in drug development aside from just establishing a recommended phase I dose. Preliminary efficacy data and confirmation of target inhibition via changes in biomarkers are now expected to be available on completion of the study. Findings of phase I trials now play a pivotal role in go-no-go decisions in drug development. Table 2 illustrates the role that early clinical efficacy signals and pharmacodynamics biomarker results obtained from phase I trials can aid in the decision process.

It is thus imperative that appropriate drugs are chosen for testing and the trials are designed and conducted in a professional and robust fashion. Patients remain our most valuable resource in drug development. Although there may be an element of altruism in patients who enter these trials, most volunteer with the hope of obtaining medical benefit as compared with available alternatives.2,23 It is crucial that the scientific community does all that is necessary to avoid putting patients onto trials that are predestined to fail because of poor science or construct. In the field of drug development, a solid preclinical foundation with good science followed with well-designed clinical studies ensures a win-win situation for both investigators and patients.

Disclosures of Potential Conflicts of Interest

References