Dose Finding of Small-Molecule Oncology Drugs: Optimization throughout the Development Life Cycle

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Abstract

In the current era of rapid marketing approval for promising new products in oncology, dose finding and optimization for small-molecule oncology drugs occurs throughout the development cycle and into the postmarketing setting. Many trials that support a regulatory application have high rates of dose reductions and discontinuations, which may result in postmarketing requirements (PMR) to study alternate doses or dosing schedules. Kinase inhibitors particularly have been susceptible to this problem, and among the 31 approved drugs of this class, the approvals of eight have included such PMRs and/or commitments. Thus, the current paradigm for dose finding and optimization could be improved. Newer strategies for dose finding rather than traditional 3 + 3 designs should be considered where feasible, and dose optimization should be continued after phase 1 and throughout development. Such strategies will increase the likelihood of a right dose for the right drug at the time of regulatory approval. Clin Cancer Res; 22(11); 2613–7. ©2016 AACR.

See all articles in this CCR Focus section, "New Approaches for Optimizing Dosing of Anticancer Agents."

Introduction

Since the approval of imatinib, the first small-molecule kinase inhibitor (KI) approved for an oncology indication, the FDA has approved 30 additional small-molecule KIs for the treatment of cancer. Given the recent history of approvals based on the results of early-phase trials driven by extraordinary efficacy data, the incentive for conducting rigorous dose-finding trials may not occur prior to marketing approval. However, the increasing need for the development of combination therapy due to resistance to monotherapy and poor long-term tolerance of approved dosing regimens, as evidenced by the frequency of dose reductions and/or interruptions (Table 1) in trials supporting marketing applications (1–4), underscores the need for a more efficient process of dose selection in the early stages of clinical development. Furthermore, the unknown efficacy in light of frequent dose reductions in the postmarket setting raises the question of whether efficacy reported in early-phase trials is accurate when applied to a real-world population. On the basis of eligibility requirements in clinical trials, the patient population in trials supporting marketing applications is healthier than the general population with the same disease; thus, the rate and frequency of dose interruptions and/or reductions may be higher in the postmarket setting. Whether the efficacy observed in clinical trials is affected by more frequent dose interruptions/reductions in the postmarket setting has not been studied vigorously and thus the answer to this question is unknown at this time.

KIs are molecules that block the action of protein kinases, which promote uncontrolled cell growth in many types of cancers (5, 6). Developers of oncology drugs are increasingly pursuing KIs as targets for oncology drugs, with 31 approved KIs on the market in the United States and many more in development. However, among these 31 KIs, eight were approved with postmarketing requirements (PMR) or commitments (PMC) to study alternate doses (Table 2) as the FDA believed that the optimal dose may not have been identified, and imatinib had a PMC to study an alternate dose in the approval for its second indication (gastrointestinal stromal tumor).

The paradigm in the oncology setting for dose-finding trials with cytotoxic chemotherapy has been to find the maximum tolerated dose (MTD) in 3 + 3 phase I trial designs. However, this strategy is a suboptimal approach in terms of characterizing the safety and tolerability of small-molecule KIs, which are given chronically and have delayed, dose-limiting adverse reactions that are not accounted for within the context of the current definitions of a dose-limiting toxicity (DLT).

To address these issues and propose new pathways for dose finding, a public workshop cosponsored by the FDA Office of Hematology and Oncology Products and the American Association of Cancer Research was convened in May 2015 in Washington, DC. The goal of the workshop was to identify best practices for integrating dose finding into the entire life cycle of product development, as this is essential to identifying the appropriate dose(s) prior to marketing.

Small-Molecule Characterization

The pharmacologic and toxicologic evaluation of KIs prior to entering the clinical phase of development is essential when
However, the full characterization of the in vitro example, the clinical adverse reactions that are associated with a KI. For potential of a KI does not necessarily give an accurate prediction of vascular adverse reactions that were observed later in clinical development. In addition, these toxicities are delayed and are unlikely to have been observed in the standard 28-day DLT window in phase I trials.

A bioinformatic and systems biology approach to predict adverse reactions observed with inhibitors with the same kinase-inhibitory profile. In this CCR Focus, Dambach and colleagues (9) discuss specific nonclinical safety-testing approaches, including a safety lead optimization and candidate identification strategy that reduces intrinsic toxicity and metabolic risk and enhances selectivity. However, the characterization of a product-specific toxicity profile should be an iterative process; as more pharmacology, pharmacokinetic, and clinical data become available, a return to focused toxicology and in vitro studies may aid in describing the mechanism of certain toxicities, as well as developing strategies to manage them in the face of promising efficacy.

### Design of Dose-Finding Trials

The most common trial design submitted to the FDA for an initial phase I, dose-finding trial employs algorithmic designs,
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As more KIs are approved, investigations into combinations are becoming more frequent. Dose optimization for small-molecule combinations may be challenging, especially for combinations of novel agents in which the optimal dose even for monotherapy may not be known. The complexity in designing the clinical development of a combination treatment comes with doubling of the pharmacology and toxicology data as well as the addition of predicting potential drug–drug interactions. Many KIs have similar toxicities, including skin and gastrointestinal toxicities, thus further complicating the development of combination therapies. High pharmacokinetic variability has been observed with KIs, and dose adjustment based on both intrinsic and extrinsic factors must be anticipated. The physiologically based pharmacokinetic approach may provide better insight into dose selection and inclusion/exclusion criteria for small-molecule combinations in clinical trials by incorporating all of these parameters to “de-risk” a combination regimen (22). Furthermore, this approach can incorporate evaluation of different degrees of tumor inhibition to dose-optimize in a phase I dose-expansion setting (12). Finally, application of pharmacokinetic/pharmacodynamic modeling may aid in dose schedule optimization with the addition of longitudinal tumor response data to determine the risk of loss of efficacy with different dosing schedules.

Integrating Dose Optimization into Clinical Development

There is a high rate of dose reductions and discontinuations due to adverse reactions in registration trials for KIs submitted to the FDA for marketing approval. Whether patients in the postmarket setting, who have a higher rate of comorbidities and more concomitant medications than the representative patients in a
clinical trial, will be able to adhere to these regimens is of great concern. It is clear that the approved dose may not be the appropriate dose for all patients, and there is a need to identify the barriers to implementing novel dose-finding approaches and optimizing trial designs more widely to overcome these barriers.

An initial step may be to redefine the DLTs for small molecules by examining the toxicities in late-phase clinical development that led to discontinuation of approved KIs. Determining when in the course of treatment and at what exposure and/or target inhibition the toxicities occurred could help to arrive at new definitions for both DLTs and DLT observation windows specific to the toxicity such that future phase I trials would be fluid evaluations of toxicity based on this knowledge. As most patients successfully treated with KIs remain on therapy for months if not years in some instances, tolerability studies beyond the typical DLT window are critical.

Model-based dose-finding trials require more support from statisticians, from both identification and incorporation of "priors" to continued assessment and input of new data throughout the trial. Thus, lack of investment in statistical human resources may be another barrier to more widespread adoption of this trial design. Furthermore, clinical investigators and Institutional Review Boards must strive to understand and embrace these trials rather than relying on the simple, algorithmic comfort of the 3 + 3 design. Finally, regulators must also encourage the use of these methodologies for more efficient dose finding.

Dose optimization for combination trials presents an opportunity for innovation and efficiency. In the current oncology drug development era, regulatory submission of a marketing application may occur as early as phase I development. However, dose optimization frequently has not been completed at this early stage and may continue into the postmarket setting (Fig. 1). Rational combinations based on biology have been identified and have proved to be additive or synergistic in preclinical models; however, success in the clinical setting has been rare, frequently due to toxicity. Many approved small molecules were developed in the MTD model and are administered continuously, and compounds with long half-lives are prioritized for ease of use. However, these qualities do not lend themselves to combination therapy, especially in light of the fear of loss of efficacy with reduced doses. Thus, the therapeutic window may not actually exist as we conceive of it in the current paradigm. This situation calls for a return to pharmacology to determine the degree and range of target inhibition and the length of time that would lead to tumor growth inhibition. This knowledge would increase willingness to embrace reduced doses and alternate dose schedules, such as intermittent dosing, alternating dosing, or continuous dosing with pulses of higher doses. Furthermore, choosing combinations in specific disease settings, such as mutant-selective KIs, may result in less overlapping toxicity due to fewer secondary pharmacology targets. Finally, one goal of combination therapy is to increase the overall exposure to combinations that may increase the duration of response. In light of this increased exposure, toxicity-monitoring windows to inform dose optimization must correspondingly increase.

Conclusions

The overriding theme for improvement is increased integration of data from all arenas of the development life cycle, including selectivity, pharmacology, secondary pharmacology, toxicology, pharmacokinetics, pharmacodynamics, and clinical data on toxicity and efficacy. With this increase in data also must come increased communication among all disciplines that contribute to dose selection and optimization; everyone from the toxicologist to the statistician to the clinical investigator should be included in dose selection discussions. Inclusion of more than one dose or up-and-down dose titration in registration trials could come from the development side, while evaluation and appropriate incorporation of these data in drug labeling could come from the regulatory side. The data and methods to improve dose finding for small-molecule KIs exist, and the challenge is for more widespread use of these methods across small-molecule KI development.

Disclosure of Potential Conflicts of Interest

P.A. Janne reports receiving commercial research grants from Astellas Pharma and AstraZeneca; royalties, through his institution, from LabCorp, has ownership interest (including patents) in Gatekeeper Pharmaceuticals; and is a consultant/advisory board member for ARIAD Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Chugai Pharma, Merrimack Pharmaceuticals, and Pfizer. A.T. Shaw is a consultant/advisory board member for ARIAD Pharmaceuticals, Daiichi Sankyo, EMD Serono, Genentech, Novartis, Pfizer, Roche, and Taiho Pharmaceutical. No potential conflicts of interest were disclosed by the other authors.

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References


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