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 I 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.*

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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

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Table 1. Dose interruptions and reductions in initial registration trials for small-molecule KIs approved for oncology indications with PMC or PMR to study alternate doses (percentage of patients on registration studies)

Drug	Dose interruption	Dose reduction	Dose interruption or delay
Erlotinib	62%	19%	NA
Vandetanib	47%	49%	80%
Cabozantinib	NA	79%	86%
Ponatinib	66%	52%	74%
Ceritinib	69%	59%	71%
Idelalisib	NA	34%	53%
Lenvatinib	56%	68%	90%

designing the phase I trial. Most KIs are promiscuous, or multi-targeted, and the perturbations of individual kinases or kinase networks lead to a variety of kinase-specific adverse reactions. However, the full characterization of the *in vitro* kinase-inhibitory potential of a KI does not necessarily give an accurate prediction of the clinical adverse reactions that are associated with a KI. For example, *in vitro* kinase profiling and toxicology studies for both ponatinib and nilotinib did not identify the thromboembolic and 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 could be a means to incorporate the collective knowledge regarding *in vitro* kinase inhibition, physiologic concentrations of the drug, and adverse reactions to identify kinase-specific adverse reactions. This approach already has been attempted by several groups, but the predictive capability of these approaches is severely compromised by the limited information available to each individual research entity (7, 8). This approach also would be bolstered by robust data-sharing initiatives among academics, regulators, and drug developers in precompetitive spaces.

In summary, the vast amount of data that is known about a new molecule before it even enters the clinic often can 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,

Table 2. Small-molecule KIs approved for oncology indications

Drug	Initial indication	Initial date of approval	Dose-related PMR or PMC
Imatinib	CML	05/10/2001	No
Gefitinib	NSCLC	05/05/2003	No
Erlotinib	NSCLC	11/18/2004	Yes
Sorafenib	RCC	12/20/2005	Yes
Sunitinib	RCC/gastrointestinal stromal tumor	01/26/2006	No
Dasatinib	CML	06/28/2006	No
Temsirolimus	RCC	03/30/2007	No
Lapatinib	Breast cancer ($HER2^+$)	05/13/2007	No
Nilotinib	CML	10/29/2007	No
Everolimus	RCC	03/30/2009	No
Pazopanib	RCC	10/19/2009	No
Vandetanib	Medullary thyroid cancer	04/06/2011	Yes
Vemurafenib	Melanoma (with BRAF V600 mutation)	08/17/2011	No
Crizotinib	NSCLC (with ALK fusion)	08/26/2011	No
Ruxolitinib	Myelofibrosis	11/16/2011	No
Axitinib	RCC	01/27/2012	No
Bosutinib	CML	09/04/2012	No
Regorafenib	Colorectal cancer	09/27/2012	No
Cabozantinib	Medullary thyroid cancer	11/29/2012	Yes
Ponatinib	CML	12/14/2012	Yes
Dabrafenib	Melanoma (with BRAF V600 mutation)	05/29/2013	No
Trametinib	Melanoma (with BRAF V600 mutation)	05/29/2013	No
Afatinib	NSCLC [with EGFR exon 19 deletions or exon 21 substitution (L858R) mutations]	07/12/2013	No
Ibrutinib	Mantle cell lymphoma	02/12/2014	No
Ceritinib	NSCLC (with ALK fusion)	04/29/2014	Yes
Idelalisib	Chronic lymphocytic leukemia	07/23/2014	Yes
Palbociclib	Breast cancer (ER/PR^+)	02/03/2015	No
Lenvatinib	Differentiated thyroid cancer	02/13/2015	Yes
Cobimetinib	Melanoma (with BRAF V600 mutation)	11/10/2015	No
Osimertinib	NSCLC (with EGFR T790M mutation)	11/13/2015	No
Alectinib	NSCLC (with ALK fusion)	12/11/2015	No

Abbreviations: ALK, anaplastic lymphoma kinase; CML, chronic myelogenous leukemia; ER, estrogen receptor; NSCLC, non–small cell lung cancer; PR, progesterone receptor; RCC, renal cell carcinoma.

such as the 3 + 3 design, with the objective of finding the MTD in a 28- or 30-day DLT observation window. The only prior data used to design these trials are toxicology data to support a safe starting dose and to design the safety observation plan based on expected toxicities. However, as noted above and in specific examples offered by Nie and colleagues in this *CCR Focus* (10), this trial design has failed to adequately predict the appropriate dose for KIs that will be given continuously and may have late-onset and/or cumulative toxicity. Furthermore, oncology development programs rarely include randomized phase II trials that examine more than one dose level or dosing regimen, and characterization of pharmacokinetics/pharmacodynamics and exposure–response relationships in early clinical trials is not consistently performed or, if performed, is not communicated to the clinical investigators prior to planning a registration trial.

The 3 + 3 design is simple in that the algorithm allows investigators to identify the MTD. However, as the MTD may not be the optimal dose with small-molecule KIs, model-based adaptive dose-finding trial designs have been held up as an alternative method. Bayesian model–based approaches allow the incorporation of historical data, such as pharmacology and toxicology, as "priors"; share information between doses; study multiple dose levels in dose expansions, including unplanned dose levels; add additional patients as needed and not in a fixed fashion; and reescalate if appropriate (11). However, this method does not recommend a particular dose for further development; instead, it allows the continuous input of data to provide better information on the risk of particular doses such that the statistician and clinical investigator can select a dose to forward in clinical development.

One method to identify the appropriate dose has been to seek the biologically effective dose; however, this method requires a biomarker by which to measure effectiveness. In hematologic malignancies, frequently there are more readily available disease measurement biomarkers in circulation or bone marrow. For solid tumors, the RECIST classification of tumor measurement is the most commonly employed to define response and progression; however, this classification uses a binary system (response vs. no response) in assessing an exposure–response relationship. The proposal to use a measurement of change in tumor size, which is a continuous data element, may provide more information in an exposure–response relationship and ultimately require fewer patients in a randomized, phase II, dose-comparison trial, thus increasing efficiency in the dose-finding endeavor (12, 13). This approach may be more difficult in phase I trials in which patients frequently are heavily pretreated, and overall response rates typically are low.

Leaders in the drug development community would agree with a move away from 3 + 3 phase I clinical trials with short windows for DLT evaluation and algorithm-based methods for KIs; the model-based approach appears to be able to incorporate more data to make more informed choices about dose selection, and the numerous methods available (Bayesian, continual reassessment method, accelerated titration design, escalation with overdose control, modified toxicity posterior intervals; refs. 14–20) should allow for better estimation of doses with which to move forward in development. The absence of the step in which this selected dose is refined in oncology in randomized phase II trials could be partially compensated for with more intensive exposure–response investigation earlier in clinical development and improved biomarkers for biologic effectiveness, as well as increased incorporation of *in vitro* and xenograft data regarding potency and pharmacokinetics for inhibition of the target.

Dose–Exposure Exploration

Dose optimization with KIs in oncology has become an abbreviated process, especially in the recent past with products receiving marketing approval based on clinical trials early in the development life cycle. However, a number of strategies can be used in clinical trials after the initial dose-finding trial to optimize the dose. Some of these strategies include testing more than one dose in phase II/III trials; employing different doses in different disease settings, especially if target inhibition data indicate that different inhibition levels are required (for example, in patients with brain metastases); considering food–drug interaction earlier in development, as exposure and tolerability of KIs may change when taken with food; considering long-term tolerability of a dose or regimen beyond the first cycle for chronic use; and considering allowing upward and/or downward dose titration. Exposure–response relationships are rarely defined with KIs; the reason for this is partly due to the lack of pharmacokinetic sampling conducted in more long-term trials in which the efficacy evaluation is the primary objective. In addition, small molecules with poor solubility frequently show high intra- and interpatient variability, making the identification of exposure–response relationships for toxicity or efficacy difficult to identify. Specific case studies are discussed by Bullock and colleagues in this *CCR Focus* (21).

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 post-market setting, who have a higher rate of comorbidities and more concomitant medications than the representative patients in a

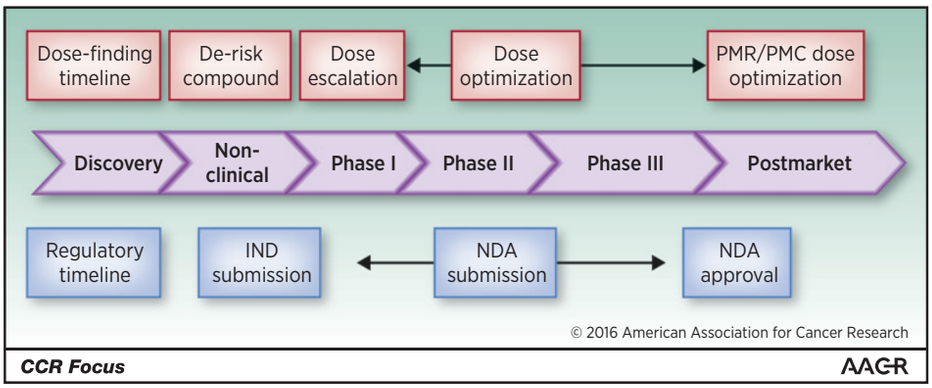

Figure 1.
In the current oncology drug development era, regulatory submission of a marketing application may occur as early as phase I development. However, dose optimization frequently has not been completed at this early stage and may continue into the postmarket setting. IND, Investigational New Drug; NDA, New Drug Application.

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 more closely 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. Jänne reports receiving commercial research grants from Astellas Pharma and AstraZeneca; royalties, through his institution, from LabCorp for intellectual property on EGFR mutations that is owned by Dana-Farber Cancer Institute and licensed to 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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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): G. Kim, R. Sridhara, A.E. McKee
Other (co-chair and planning committee member of workshop from which this manuscript originated): A.E. McKee

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