The Changing Landscape of Phase I Trials in Oncology

Kit Man Wong, MD, Anna Capasso, MD, and S. Gail Eckhardt, MD

There has been an exponential rise in the number of novel anticancer drugs in development over the last decade. Our improved understanding of the molecular mechanisms of tumorigenesis has driven the discovery of molecularly targeted agents (MTAs) that inhibit specific proteins or pathways. However, although over 750 anticancer drugs are presently in development,[1] only 5% of these ultimately demonstrate sufficient efficacy for regulatory approval and clinical application.[2] For example, from 1998 to 2014, the failure-to-success ratio of investigational agents for melanoma was 14:1, whereas only 10 of 177 agents for lung cancer were approved.[3] Furthermore, the drug developmental process in oncology is estimated to take 1.5 years longer than in other diseases.[4] This highlights the need to maximize the efficiency and cost-effectiveness of early clinical trials, given the vast resources and time involved.

A phase I trial represents the critical transition of a novel compound from the preclinical to clinical stage, and thus provides the foundation for an efficacious drug development program. Several aspects of phase I trials have evolved in the era of MTAs that span multiple facets, from the overarching goals of phase I studies to trial design and the regulatory process, with consequent implications for participating institutions and investigators. This article summarizes the changing landscape of phase I trials in oncology, new challenges, and future directions.

TRIAL DESIGN

The conventional goals of phase I trials are to characterize the safety, tolerability, and maximum tolerated dose (MTD) of a novel agent by enrolling patients with a wide range of advanced cancers refractory to standard therapy. With the emergence of MTAs, new approaches related to dose escalation, patient selection, and study endpoints are making their way into current phase I studies.

Dose Escalation

The classic 3 + 3 design is a simple algorithmic method consisting of a set of predefined dose escalation rules based on the observed rate of dose-limiting toxicities (DLTs) within a specified window of assessment, typically 28 to 30 days. This approach enrolls cohorts of three patients at each dose level based on an algorithm (Table 1). The MTD is defined as the dose level at which the DLT rate is less than 33% and is usually the recommended phase II dose (RP2D) for further study. This design is well suited for cytotoxic agents, which are characterized by a positive correlation between dose, toxicity, and efficacy, and the highest dose with acceptable toxicity is desired.[5]

Although the 3 + 3 design is simple to implement, it may lead to suboptimal treatment in a large number of patients.[6] The estimated MTD may be imprecise because of the small cohort size and the nature of a rule-based approach.[7] Furthermore, MTAs may demonstrate delayed or cumulative mechanism-based toxicities that are not captured within the DLT assessment window. In these cases, the maximally administered dose is determined instead of the MTD.[6] In a systematic review of more than 450 phase I trials, the MTD was identified for 64% of MTAs compared with 99% of cytotoxic agents.[8] It is estimated that 20% of dose reductions with MTAs occur beyond cycle 1, the usual DLT assessment period.[9] Indeed, there is great heterogeneity in the DLT definition across published phase I trials of MTAs, particularly with respect to the window of assessment and severity.[10] In fact, the RP2D of MTAs should incorporate toxicity data from all cycles of therapy and symptomatic grade 2 toxicities.[9,11]

New strategies for dose escalation were developed to address these issues, including accelerated titration and model-based designs (Table 1). The accelerated titration design (ATD) as originally proposed consists of an accelerated phase of 100% dose escalation steps in successive single-patient cohorts, until DLT or substantial toxicity occurs during any cycle, at which point the trial reverts to the standard

From the Developmental Therapeutics Program, Division of Medical Oncology, Department of Medicine, University of Colorado, Aurora, CO.

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Corresponding author: S. Gail Eckhardt, MD, Anschutz Medical Campus, University of Colorado Cancer Center, 12801 E. 17th Ave., L18-8111, Campus Box 8117, Aurora, CO 80045; email: gail.eckhardt@ucdenver.edu.

3 + 3 scheme with smaller dose increments.[12] Not only does the ATD enable faster dose escalation without increased toxicity, it also allows more patients to be treated at the therapeutic dose.[12,13]

Model-based adaptive designs were devised to capture delayed toxicities without prolonging patient accrual. The continual reassessment method (CRM) requires a priori estimation of the dose-toxicity model, which is continuously updated by incorporating the cumulative toxicity data from all treated patients to compute the optimal dose for the next cohort.[5,14] Therefore, late onset toxicities are considered in subsequent dose level determinations. Several modifications have been made to the original CRM to further enhance safety or flexibility, such as sequencing 3 + 3 and CRM,[15] the quasi-CRM for nondichotomized toxicity grades,[16] the time-to-event CRM for very late toxicities as observed postradiation,[17] and other extensions to handle subject heterogeneity or varying treatment schedules.[18] Although the CRM is advocated, it requires a close collaboration between the investigator and biostatistician throughout the dose escalation phase.

The efficiency of novel dose escalation designs was demonstrated in a study of 84 phase I trials from 2000 to 2010. Compared with the traditional strategy, new designs explored a greater number of dose levels (median of 6, 8, and 10 levels for 3 + 3, ATD, and modified CRM, respectively) and achieved a higher mean MTD-to-starting dose ratio (ratios of 9, 22, and 30, respectively).[19]

The changes in dose escalation in phase I trials have resulted in fewer patients enrolled per dose level. This presents a challenge to multi-institutional studies, as individual sites enroll very few patients, not only preventing investigators from gaining adequate experience with a drug and its toxicities, but also limiting the number of patients sampled for pharmacokinetic (PK) and pharmacodynamic (PD) studies. Greater communication between sites also is necessary to completely capture the toxicity data for dose escalation decisions. Therefore, in some respects, the multisite nature of current phase I trials may drive the continued use of more traditional designs.

KEY POINTS

- Several aspects of phase I trials have evolved in the current era of molecular targeted agents to adapt to the changing nature of anticancer therapy and to increase the efficiency of drug development.
- Current phase I designs are increasingly integrating novel dose-escalation approaches and biomarker-driven selection of patients, as well as expanding study objectives to include the evaluation of efficacy and pharmacodynamics/pharmacokinetics in addition to safety.
- Changes to the regulatory approval process have helped to expedite drug development, particularly for novel agents with a strong biologic rationale and proof of concept, validated predictive biomarker, and clear evidence of efficacy in early trials.
- As a result of the substantial changes in phase I trial goals and conduct, there is a parallel shift toward multi-institutional trials and central study management by clinical research organizations.
- The use of multi-institutional trials has a significant impact on the structure of phase I programs and the experience of investigators, particularly because of limited patient enrollment at each site.

Patient Selection

Rather than a single dominant gene, it is now recognized that most cancers arise from multiple somatically mutated oncogenes, each contributing a small effect, which accumulate during tumor progression. Thus, even within the same cancer type, individual tumors are driven by distinct sets of genes and pathways.[20] It is this genetic heterogeneity that underlies the observed variable responses to MTAs.

In most cases, an MTA is active only in a subgroup of patients who may be identified using predictive biomarkers, such as the expression level of a gene or protein, or the presence of a gene mutation, amplification, or translocation. Phase I trials increasingly are used as a platform to explore biomarkers and enrich molecular subsets of patients most likely to respond to specific MTAs. When used appropriately, this can improve the efficiency and safety of drug development.[21] For instance, the successful use of biomarker-driven patient selection was exemplified by the phase I trials of crizotinib (PF-02341066) in EML4-ALK rearranged non-small cell lung cancer[22] and vemurafenib (PLX4032) in BRAF V600E mutant melanoma,[23] in which the remarkable responses in these patient subsets helped to accelerate their approval.

However, challenges are inherent in incorporating biomarkers in early drug development.[5] As most cancers have multiple genetic aberrations, sensitivity to an MTA is likely modulated by many factors. Also, identifying a reliable biomarker may be less feasible when an agent has several targets, as is the case with most tyrosine kinase inhibitors. Since the misapplication of predictive biomarkers can potentially be over-restrictive and exclude patients who might benefit from an MTA, establishing a very strong scientific basis for the biomarker with preclinical validation is a prerequisite, as is acceptable sample collection, assay performance, reproducibility, and standardization.[24-28] For these reasons, biomarkers typically are investigated as exploratory objectives.

The increasing use of biomarker-based patient selection has transformed the enrollment process of phase I trials. First, patients must be molecularly screened to determine their eligibility. Where the biomarker of interest has a low prevalence, many patients must be screened to identify a few potential candidates, and more studies have to open at a single center to accommodate all patients wishing to enter a trial. Phase I teams must be highly organized to obtain archival tissue or fresh biopsies in a timely manner and be prepared to manage patient anxiety from invasive screening procedures and negative results. Furthermore, since many

Table 1. Comparison of Dose Escalation Designs

	Algorithmic Design (3 + 3)	Accelerated Titration Design	Model-Based Design (Continual Reassessment Method)
Dose levels	Predefined starting dose level (considered safe in humans based on data from animal models) and DE steps	Predefined starting dose level (considered safe in humans based on data from animal models); DE steps determined by occurrence of DLT	Starting dose level based on a prior dose-toxicity curve and target DLT rate; dose of next cohort determined by the updated model using the same target DLT rate
Number of patients per cohort	3 patients in each cohort; 6 patients in an expanded cohort	1 patient in each cohort during the accelerated titration phase; 3 or 6 patients in each cohort once DE reverts to standard 3 + 3	Number specified by the investigator, typically 2 patients per cohort
DE scheme	Patients are enrolled (3 at a time) in each successive cohort. When 1 out of 3 patients has DLT, the cohort is expanded to 3 more patients at the same dose level. If 2 or 3 patients in a cohort have DLTs, the next lower dose level is expanded to 3 more patients.	During the accelerated phase, DE steps occur at 100% increments until one DLT or two moderate toxicities occur at any cycle. Then, DE reverts to the standard 3 + 3 design with 40% DE steps.	The dose-toxicity model is updated on an ongoing basis using the cumulative toxicity rate from all previously treated patients to determine the optimal dose level of the next cohort using the same target DLT rate
MTD	Dose level at which there is ≤ 1 DLT out of 6 patients (< 33%)	Dose level at which there is ≤ 1 DLT out of 6 patients (< 33%)	Dose corresponding to the predefined target DLT rate based on the final updated model
Advantages	- Simple, easy to implement	- More patients treated at the therapeutic dose	- More patients treated at the therapeutic dose
	- Does not require statistical modeling	- Faster DE and MTD reached with the same number of patients	- Model-based approach allows more accurate estimation of MTD
	- Allows conservative DE for drugs with narrow therapeutic index		- Takes into account delayed toxicities
Disadvantages	- Many patients may be treated at subtherapeutic doses	- May not be appropriate for agents with narrow therapeutic index	- Continual modeling by a biostatistician is needed
	- MTD may be imprecise		
	- May not be appropriate for MTAs with no or delayed toxicities		

Abbreviations: DE, dose escalation; DLT, dose-limiting toxicity; MTA, molecularly targeted agent; MTD, maximum tolerated dose.

biomarkers are disease-specific, centers must be able to rapidly screen large numbers of patients for disease-specific expansion cohorts, which may pose a challenge when the phase I program is not well integrated with subspecialty clinics. Finally, each patient in need of an experimental therapy has to be considered for multiple studies at the same time to avoid delays in entering a trial in the event of a screen fail. Strategies to facilitate the inclusion of molecularly selected patients are needed, such as molecular prescreening programs for all metastatic patients to ease the transition to a phase I trial on disease progression.[29]

Endpoints

The conventional primary endpoint of phase I trials has been toxicity, with efficacy as only a secondary outcome. However, with the new breakthrough therapy designation created by the U.S. Food and Drug Administration (FDA) to expedite drug development, obtaining early evidence of efficacy is now an important component of phase I studies. This has increased the use of tumor-specific expansion cohorts to further characterize both safety and clinical response at the RP2D,[30] which is associated with a higher success rate of phase II trials and faster drug approval.[31] As mentioned above, the organization of some phase I centers also has been restructured around disease-specific investigators and clinics.

Moreover, in the MTA setting, the use of toxicity as the primary determinant of the RP2D has been called into question.[32] Unlike cytotoxic agents, the efficacy of MTAs may not be reliably predicted by either dose or toxicity. Increasingly recognized for MTAs are mechanism-based toxicities that relate to the presence of the target on normal tissues and cause chronic toxicities.[33] Although not always dose-limiting, the latter may nonetheless be compliance-limiting (e.g., rash, diarrhea, fatigue). These and other physiological adverse effects of MTAs (e.g., hypothyroidism, hypertension) require the parallel development of supportive care regimens and collaboration with other medical specialists for optimal clinical development.[34-37]

For MTAs, alternate endpoints reflecting target modulation may be more relevant surrogates of efficacy when determining the RP2D, and they may assist in prioritizing drug candidates for further development.[38] Therefore, the PD analysis of MTAs has become an integral part of phase I trials. Common correlative endpoints include protein expression in tumor tissue by immunohistochemistry before and after treatment, which requires invasive tissue acquisition procedures, as well as less invasive assays of serum proteins, peripheral blood mononuclear cells, and imaging biomarkers.[5,6] Circulating tumor cells and DNA will likely play an important role in the future as liquid biopsies.[39,40] Moreover, PK endpoints are often simultaneously analyzed to charac-

terize the PK-PD and PK-toxicity relationships, which can guide the selection of the RP2D when the plasma drug concentration for maximal biologic effects is known.[32,41] Well-planned correlative endpoints can significantly improve the efficiency of drug development and reduce overall costs.[38]

Therefore, although the evaluation of safety remains the primary goal of early phase studies, assessment of efficacy and PD/PKs also are key objectives in this new era of drug development. This, in turn, is transforming the landscape of phase I trials, with greater emphasis on disease-focused clinicians, tissue acquisition and assay performance, multidisciplinary supportive care, and radiological expertise in functional imaging.

REGULATORY CHANGES

The development of a successful drug from first-in-human study to approval normally takes about 7 years, during which its safety and efficacy are thoroughly and rigorously assessed.[42] However, in the case of MTAs with a clearly established biologic mechanism backed by proof of concept, unprecedented clinical responses with minimal toxicity, and availability of a strong predictive biomarker, many argue that the approval process should be shortened, especially when promising results are observed in early phase. Strategies to expedite drug development were proposed in the FDA Safety and Innovation Act of 2012. Thus, the new breakthrough therapy designation for investigational drugs was added to FDA's armamentarium of programs that also include the fast-track designation, accelerated approval pathway, and priority-review designation (Table 2).[43]

The opportunity to exploit such pathways has a substantial effect on phase I trial conduct. Not only are efficacy endpoints emphasized in the design, the quality of data is increasingly scrutinized because it may be used for a new drug application. In fact, trials frequently are now managed by large clinical research organizations (CROs) to standardize trial conduct and data collection.

PRACTICAL IMPLICATIONS

Over the past decade, phase I trials have evolved from single-/oligo-site studies to increasingly large multi-institutional efforts with the goal of expediting patient accrual. In the latter, three or more institutions typically enroll patients, and slots in each cohort are assigned by the sponsor or filled on a competitive first-come first-served basis.

Multi-institutional trials have several implications, including limited slot availability per site, thus requiring more trials to be opened at a center to accommodate the same number of patients. Moreover, additional staff, resources, and frequent conference calls among participating sites are needed to enable real-time notification of adverse events and DLTs. These factors have led to greater reliance on CROs for study management. Further, the desire to accelerate patient recruitment results in the selection of sites based on their ability to enroll rather than on the experience and quality of the phase I program.

Similarly, the experience of phase I investigators has been influenced by multi-institutional trials. An individual investigator at one site can only gain limited clinical experience with a novel agent and its spectrum of toxicities.[8] Moreover, since sponsors and/or CROs are usually responsible for overseeing the operations of current phase I trials, it is a challenge for trainees and junior faculty to obtain comprehensive training in early drug development. Consequently, many years

Table 2. Main Features of the FDA's Expedited Programs for Serious Conditions

	Qualifying Criteria	Features
Fast track designation	A drug that is intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address unmet medical need	- Actions to expedite development and review - Rolling review
Breakthrough therapy designation	A drug that is intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on clinically significant endpoint(s) over available therapies	- Intensive guidance on efficient drug development - Organizational commitment - Rolling review - Other actions to expedite review
Accelerated approval pathway	A drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than IMM that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)	- Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit
Priority review designation	An application (original or efficacy supplement) for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness	- Shorter time for review of marketing application (6 months compared with the 10-month standard review)

Abbreviations: FDA, U.S. Food and Drug Administration; IMM, irreversible morbidity or mortality.
Adapted from: U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for industry: expedited programs for serious conditions-drugs and biologics. May 2014. www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. Accessed December 27, 2014.

of experience may be required before they are fully competent in designing and carrying out phase I studies, highlighting the importance of strong mentorship in this setting. At the same time, it has become more difficult for junior faculty to be truly independent investigators of phase I trials and advance their academic careers. This is especially true at smaller centers that lack the capacity to compete for enrollment. Therefore, although multisite trials have the advantage of improving efficiency, these issues have led some to suggest that no more than three centers participate.[5]

CONCLUSION

Phase I trials are the cornerstone of developmental therapeutics, and they are playing an expanding role in the changing landscape of cancer drug development. In the era of MTAs, they have evolved into complex studies that provide much more information than merely safety. With different dose escalation designs, molecular patient selection, and alternate endpoints, not only can current well-designed phase I trials better determine the RP2D of an MTA, they can also provide an opportunity to demonstrate proof of concept, characterize PD/PKs, define predictive biomarkers, and explore early efficacy that may potentially expedite drug approval. Importantly, this has led to a shift toward multi-institutional trials and CROs, greater demand on individual sites in terms of patient screening and enrollment, and the need to open more studies at each center.

Coupled with FDA initiatives to accelerate drug approval, current phase I studies can greatly advance the drug development process, as evidenced by the success of recently approved MTAs. In fact, the landscape of phase I oncology trials is ever-changing. As we continue to discover new molecular targets and better therapies, phase I trials must continue to evolve to efficiently translate these innovative therapies from bench to bedside.

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