Phase 0 Clinical Trial Strategies for the Neurosurgical Oncologist

In an era of escalating drug discovery costs, shifting priorities within the pharmaceutical industry, and longstanding challenges in central nervous system drug delivery, surgical trials offer an avenue to identify promising agents with demonstrable tumor penetration and molecular effects. The rise of pharmacodynamic- and pharmacokinetic-driven clinical trials, including phase 0 study designs, creates an opportunity for the neurosurgical oncologist to engage drug development for brain tumor patients directly. Here, we review the phase 0 clinical trial mechanism as well as its current and future applications within neurosurgical oncology.

KEYWORDS: Pharmacokinetics, Pharmacodynamics, Phase 0, Phase 0/2, Glioma, Clinical trial

Preclinical studies are an essential component to drug discovery and drug development for human cancer. In non-central nervous system (CNS) cancers, animal models can serve as reliable surrogates that adequately portray the human disease. For brain tumors, however, there are no consensus choices for preclinical models and a variety of approaches are routinely employed, including in vitro progenitor cell cultures, chemically induced syngeneic models, xenograft models, organoid models, and transgenic animals. These strategies do not completely replicate tumor progression.1-6 Patient-derived xenograft models are also used to predict drug responses for brain tumor patients by serving as patient “avatars.”7 This approach, however, is limited by low engraftment and growth rates, dependence on immunodeficient mice, species-specific difference in the blood–brain barrier (BBB), insufficient intratumoral genomic heterogeneity, and incomplete recapitulation of the tumor microenvironment. Taken together, these limitations can hamper new drug development for brain tumors.

In March 2004, the US Food and Drug Administration (FDA) reported concerns that excessive development costs were preventing new drugs from reaching patients at an affordable price. In response to an FDA report entitled “Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products,” new rules were developed to reduce the time and resources needed to separate promising candidate drugs from those with less promise. The FDA announced the creation of the Exploratory Investigational New Drug (IND) mechanism (aka, the phase 0 clinical trial).8-10 This new mechanism, distinct from, and not always preceding, phases 1, 2, or 3, enables investigators to presurgically dose patients with an experimental agent in order to identify drugs that penetrate the tumor and modulate the intended molecular target(s). This new mechanism could fast track early-phase drug development and accelerate the efficiency of ensuing later-stage trials.

Phase 0 trials identify promising new drugs by “humanizing” preclinical studies. An array of design variations exists under the phase 0 umbrella to address a range of possible study objectives (Table 1).11,12 These include studies to perform the following: (1) determine whether a mechanism of action (MOA) defined in nonclinical models is achievable in humans13,14; (2) refine a biomarker assay using human tumor
tissue; (3) develop a novel imaging probe and evaluate its distribution, binding characteristics, and target effects in humans; (4) evaluate the human pharmacodynamics (PD) and/or pharmacokinetics (PK) of 2 or more analogs to select the most promising candidate for further development; (5) determine a dose range and sequence of administration of a biomodulator for use in combination with established chemotherapies; and (6) provide human PK-PD relationship data for an agent before phase 1 testing. For CNS oncology studies, PK analysis refers to measurement of study drug concentration in brain tumor tissue and PD analysis refers to quantification of a molecular/cellular target influenced by the study drug.

For all phase 0 studies, the drug doses administered are pharmacologically active, but subtherapeutic, and the experimental agent is given only to a small number of patients (typically 10-15). Because of the limited dosing (a “microdose” is used and defined as <1% of the therapeutic dose), investigators can anticipate a low clinical risk to participants, and thus, the preclinical toxicology studies necessary to support an exploratory IND are less extensive than those needed for traditional INDs (phase 0 studies can be supported by either mechanism). Importantly, phase 0 studies do not generate safety and tolerability data like that obtained from conventional phase 1 studies, nor do they provide evidence of clinical efficacy on their own (Table 2). Thus, phase 0 trials do not replace the need for conventional phase 1, 2, or 3 studies. However, they can inform and accelerate the decision to pursue such studies by providing a proof of concept in addition to PK and PD data, which subsequently shorten the drug development timeline.

In 2009, the National Cancer Institute reported their initial experience with a phase 0 clinical trial using an exploratory IND mechanism. This non-CNS study sought to determine if an investigational poly (ADP ribose) polymerase inhibitor, ABT-888, modulated its intended target. Kummar et al reported that 13 patients “with advanced [non-CNS] malignancies received the study drug; nine patients underwent paired tumor biopsies.” Five months after the start of the study, investigators “obtained pivotal biochemical and pharmacokinetic data that have guided the design of subsequent phase 1 trials of ABT-888 in combination with DNA-damaging agents.” In November 2016, ABT-888 (known as veliparib) received orphan drug status for non-small cell lung cancer. Since the ABT-888 study, a number of clinical trials containing both PK and PD endpoints have been reported in the neuro-oncology literature. Although many of these studies do not self-identify as phase 0 trials, they meet a working definition of a phase 0 brain tumor study: a prospective surgical trial incorporating simultaneous PK and PD analyses of posttreatment brain tumor tissue. The most recent addition to this growing literature is a phase 0 trial for recurrent glioblastoma patients examining the impact of a first-in-class Wee1 inhibitor. Interestingly, for the drug of interest (AZD1775), an animal study preceded the phase 0 trial and reported minimal activity of the agent across the BBB. Nevertheless, the drug’s physicochemical properties suggested suitability for CNS penetration. To resolve this controversy, a phase 0 study was conducted in 20 patients who received a single dose of AZD1775 prior to planned recurrent glioblastoma resection (Figure 1). In contrast to preclinical data on the experimental agent, this phase 0 trial revealed excellent human brain tumor penetration and provided the first evidence of drug activity in glioblastoma patients.

THE BBB AND PK

Insufficient penetration of therapeutic agents across the BBB is a central obstacle to the successful treatment of brain tumors. Contemporary efforts to predict CNS penetration are inconsistent but focus on 3 central mechanisms driving CNS penetrations: (1) passive membrane permeability, (2) facilitated transport at the BBB, and (3) tissue binding between the brain and plasma (or blood) compartments. Despite several in vitro cell-based models that calculate BBB permeability, metabolism, and transporters, the in vivo system is still incompletely reproducible. Efforts to simulate the human BBB in silico have been inconsistent in predicting BBB permeability, in part due to the broad range of species-specific efflux and uptake transporters that actively modulate the transport of substrate drugs. Similarly, animal models, as well as extrapolations from human cerebrospinal fluid (CSF) studies, are limited in their predictivity. Preclinical modeling for brain tumors is also hampered by the dynamic influx/efflux transporter system at the BBB, the lack of accepted biomarkers and/or surrogate measures of drug activity/response, and the limited strategies to assess drug exposures in the brain. For the latter, physiologically based pharmacokinetic (PBPK) modeling of the CNS can provide an opportunity to predict relevant drug concentrations at the therapeutic target site, and in vitro-in vivo extrapolation linked with PBPK is a strategy being refined to quantitatively bridge
### TABLE 2. Phase 0 Study Design Modifications for Brain Tumor Patients

| Conventional Phase 0 Study Design Elements | Phase 0 Study Design Modifications for Brain Tumors |
|-------------------------------------------|---------------------------------------------------|
| May be first in human                     | No change                                         |
| No therapeutic or diagnostic intent       | No change                                         |
| Limited number of patients                | No change                                         |
| Presurgical drug microdosing              | Presurgical subtherapeutic dosing (e.g., MTD for 1 to several days) |
| Simultaneous PK and PD measurements in plasma and tumor tissue | Simultaneous PK and PD measurements in plasma, CSF, and tumor tissue. |
| Precedes traditional phase 1 dose escalation, safety, and tolerance study | Follows phase 1 study, may include PK- and PD-dependent phase 2 component |
| Multidisciplinary trial team may not require a surgeon | Neurosurgeon integrated into the multidisciplinary trial team |

![Diagram](image)

**FIGURE 1.** AZD1775 phase 0 clinical trial study for recurrent glioblastoma. A dose-escalation arm (above) employed 3 dose levels for a single dose of the experimental agent. A time-escalation arm (below) included a single dose level but varied the interval from dosing to surgical resection. These schemas represent the trial design, not the clinical course of individual patients.

in Vitro and in Vivo data from such trials. This hybrid modeling strategy does not replace the need for phase 0 trialing but identifies key mechanisms dictating the PK and tumor penetration properties of study drugs that can be used to select drugs for clinical analysis.

Conventional microdosing strategies facilitate drug development by reducing the risk of adverse effects and by minimizing the need for preclinical pharmacokinetic and toxicology studies that may later be refuted by the clinical trial. From a regulatory perspective, establishing a microdose in humans requires only a single species in the preceding animal studies. Ultrasensitive analytical methods, often using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS), must be available to measure drug and metabolite concentrations in the low picogram to femtogram range. Microdosing strategies are also ineffective for agents with nonlinear kinetics or agents with...
differences in solubilities at therapeutic doses. For brain tumor patients, the central limitation of microdosing relates to the BBB. Specifically, drug microdoses that may be detectable in plasma using modern analytical methods are often undetectable within the CNS. Consequently, brain tumor phase 0 studies require higher systemic drug concentrations for detection across the BBB. Recent studies have navigated this challenge using a higher dose, “subtherapeutic” dosing strategy that employs a drug’s maximally tolerated dose but administers the drug for as briefly as a single day. This specialized tactic, although contrary to the conventional “microdose” design of non-CNS phase 0 trials, maximizes the opportunity for CNS penetration while minimizing the risk of adverse drug events in phase 0 studies for brain tumor patients. This approach does, however, require a phase 1 dose-finding study in advance.

For brain tumor phase 0 studies, specialization in CNS PK is essential. Commonly, the total brain-to-plasma concentration ratio (Kp) is reported in the literature as a measure of drug-brain penetration. However, Wu et al report that Kp’s applicability to PK is somewhat limited, as Kp is largely driven by “nonspecific binding of a drug to proteins and lipids in plasma and [the] brain.” Further state that because “unbound drug concentration drives the in vivo pharmacological effect, the use of unbound brain-to-plasma concentration ratio (Kp, uu, [brain]) as a measure of brain penetration is more pharmacologically relevant.” Thus, for brain tumor phase 0 studies, both total and unbound drug concentrations in plasma and tumor tissues should be measured, typically using an equilibrium dialysis method combined with LC-MS/MS analysis.

PK analysis of a study drug’s level of brain tumor penetration requires consideration of concomitant medical regimens in the perioperative and intraoperative intervals. Routine preoperative medications for brain tumor patients include corticosteroids and antiepileptic drugs that can enhance the adverse effects of experimental agents, interfere with drug metabolism, and confound subsequent PK analyses. Furthermore, traditional neuroanesthetic regimens often include contraindicated agents that must be adjusted depending on the study drug’s MOA and metabolism. Although the impact of some concurrent medications can be compensated for at the time of PK calculations, the relatively small sample size of phase 0 studies necessitates the optimal selection of perioperative and intraoperative medications for brain tumor patients. The choice of operative strategy, including the need for conscious sedation in awake craniotomies, adds a level of complexity for select patients.

**DRUG SELECTION AND PD**

Not all novel agents are appropriate for phase 0 studies, and not all phase 0 studies are first in human. Drug candidates suitable for phase 0 testing typically meet several requirements: (1) the mechanism of action is known, (2) successful development of the drug is predicated on a PD endpoint; (3) modulation of the drug target in preclinical studies is associated with an antitumor effect; (4) the drug’s therapeutic window (ie, the dose range associated with nontoxic, yet effective, treatment) is wide; (5) modulation of the drug target is anticipated at nontoxic doses and over short durations of exposure (≤7 d); and (6) target modulation is likely determined with a small sample size (typically <10-15 patients).

Drug selection of “promising” agents for phase 0 studies should be assessed in the context of the proposed agent(s). For single-agent strategies, a phase 0 trial can perform the following: (1) assess the target effects in tumor biopsies obtained pre- and postexposure; (2) refine biomarker assays associated with drug effects in tumor, blood, and other surrogate tissue; and (3) approximate the safe but potentially effective starting dose using a small number of patients. For combinatorial drug strategies employing 2 targeted agents or a targeted agent plus a conventional cytotoxic agent, phase 0 studies can assess the modulatory effects of one drug or both and determine their relative schedule and sequence. In this respect, “promising” agents may be defined in a number of ways, but many share one or more of the following characteristics: (1) first-in-class molecules, (2) target mechanisms previously unexplored in neuro-oncology, (3) evidence of exceptional effects in non-CNS disease, and (4) mechanistic or toxicity characteristics well suited for combined drug therapy.

Accompanying the drug selection process is the identification of a suitable biomarker-based PD assay to evaluate drug effect(s). Because this test is a readout for the drug’s molecular effects, it is most relevant when it measures a proximal downstream event in the drug’s putative MOA. The assay is initially characterized and validated in the preclinical setting using techniques that approximate those in the clinical setting. The most suitable PD biomarkers for phase 0 trials are robust and consistently detected in uniformly handled tissues. In some circumstances, this assay will ultimately serve as the basis for future clinical development decisions.

Phase 0 studies for non-CNS cancers often employ multiple biopsies before and after drug exposure as part of the tumor PK and PD analyses. Depending on the study drug’s MOA and molecular target, surrogate tissue specimens such as skin biopsies can also be used instead of tumor tissue samples. In contrast, brain tumor phase 0 studies rarely include predrug tumor tissue biopsies, owing to the added risk, cost, and time of such procedures, and there are no known surrogate tissues that accurately correspond to brain tumor tissue. Instead, such phase 0 studies typically rely upon archival tissue from a single timepoint prior to phase 0 study enrollment to serve as the baseline comparator. This strategy limits phase 0 studies to brain tumor patients undergoing planned re-resection of tumor recurrence. Additionally, because the time between these 2 samples can be months to years, often encompassing the use of other adjuvant therapies, the dependability of an archival tissue sample as a predrug baseline is less than ideal. Although these limitations are likely unavoidable in phase 0 trials for brain tumor patients, the study design may be optimized by first assessing PD endpoints in a reference population of matched samples from the initial diagnosis and recurrence. Only PD biomarkers that are stable in expression and function across this interval are acceptable as PD endpoints.
STUDY LIMITATIONS AND ETHICAL IMPLICATIONS

Although PK- and PD-driven clinical trials provide early insight into human biological responses, their level of scientific rigor falls short of the conventional preclinical basic science studies. Phase 0 studies can contextualize drug-related pharmacological and molecular responses in the patient setting, but practical limits of tissue accrual, experimental timing, and other clinical and surgical variables exist. Control specimens are also not as reliable here as they are in preclinical models. Furthermore, the heterogeneity of tumors such as gliomas adds an additional dimension of complexity, as the integrity of the BBB is not uniformly disrupted in these lesions, nor is a tumor’s molecular biology landscape evenly distributed. To this end, sampling error remains an additional challenge to interpreting results, although it can be lessened through multicompartment tissue acquisition. Thoughtful study design and execution are necessary to navigate these limitations, but, ultimately, they are part and parcel with this trial strategy and delineate how subsequent phase 1, 2, or 3 studies remain essential.

The nontherapeutic nature of phase 0 trials has ethical implications as well. For early-phase clinical trials, investigators and subjects typically view clinical research in the context of treating illness. In phase 0 trials, however, the subjects are helping investigators answer a scientific question. Emphasizing this point can reduce misunderstandings and calibrate expectations. From an ethical perspective, clinical research should be conducted only when the risks and burdens to subjects are both minimized and justified by the potential benefits. Therefore, according to Abdoler et al.49,50 “clinical trials that do not offer the possibility of medical benefit but expose subjects to some risk for the benefit of others can be ethically permissible.” Patient safety data from phase 1 trials, as well as the assumption that risks associated with phase 0 trials are lower, suggest patient risk in phase 0 studies is acceptable. Subsequent trials incorporating data from phase 0 studies may experience fewer toxicities and higher rates of clinical benefits, thereby enabling such patients to derive benefit from the preceding phase 0 study. Phase 0 trial participation should also be designed to avoid adversely affecting a patient’s eligibility for subsequent therapeutic trials.11 Murgo et al11 stated that “receiving a drug as part of a phase 0 trial should not prohibit the patient from enrolling in other protocols with that agent or class of agents.” Because these trials are nontherapeutic and involve minimal drug exposure for patients, patients do not need to wait the standard “washout” period after the study, prior to entering another trial employing an unrelated experimental therapy.11

PHASE 0/2 CLINICAL TRIAL DESIGN

For brain tumor patients, phase 0 clinical trials are challenging, not only due to trial logistics, but also because of the dampening effect the nontherapeutic nature of such studies has on patient accrual. A phase 0/2 trial adapts the phase 0 strategy to brain tumor patients but incorporates a PK- and PD-dependent trigger that graduates phase 0 patients into an exploratory phase 2 study arm (Figure 2). This arm is not powered for efficacy, but rather provides an opportunity to observe longitudinal therapy in a highly selected population and to query changes in tumor biology accompanying experimental drug resistance. In doing so, this tactic is compelling to potential brain tumor patients by providing them with the confidence that, if selected for treatment, there is biological evidence suggesting their tumor can respond. For these patients graduating to phase 2, they (and their providers) are motivated by the biological rationale connecting the experimental therapy to their individual cases.

Less than 1% of all published clinical trials for brain tumors contain both PK and PD endpoints evaluating tissue effects following initial drug exposure. Fewer studies, however, examine tissue from these same patients following extended periods of drug treatment, even though 19% of all high-grade glioma patients, for example, undergo 3 or more tumor resections.51 Using the phase 0/2 study paradigm, patients with planned resections for tumor recurrence following therapeutic dosing of the experimental agent(s) provide an opportunity for longitudinal tissue analysis. Within this population, enhancing and nonenhancing tumor tissue from fast- vs slow-recurring tumors can be compared to identify the roles of on-target and off-target pathways in tumor escape. To control for interindividual variations in CNS drug penetration, putative resistance mechanisms can also be examined in matched tissue specimens from initial, second (phase 0), and third (phase 2) resections. Beyond characterizing resistance mechanisms, planned identification of tissue biomarker signatures associated with susceptibility to experimental agents can inform future clinical trial designs. For patients completing the phase 0 component of the study with evidence of adequate tumor penetration (ie, a “positive” PK endpoint), variations in observed PD effects provide an opportunity to distinguish biological responders (ie, patients with positive PK and PD endpoints) from nonresponders (ie, patients with a positive PK endpoint and negative PD endpoints). Using a variety of molecular and genetic techniques, a menu of tumor biomarker combinations predictive of pharmacodynamic sensitivity to the study drug(s) can be formulated for prospective interrogation. Taken together, these longitudinal studies of human brain tumors exposed to experimental therapies can provide actionable evidence for future strategies.

The phase 0/2 clinical trial design is a step towards controlling for the structural and functional heterogeneity of human brain tumors in prospective therapeutic trials. Simply put, only patients with demonstrable in Vivo drug effects are graduated to therapeutic dosing. Those who do not demonstrate an adequate drug response are identified within days of their neurosurgical resection, allowing them to pursue other, more traditional clinical trial options following recovery from surgery. The risk of the study to patients with negative study results is negligible, owing to the subtherapeutic dosing regimen during the preoperative phase.
FIGURE 2. Sample phase 0/2 clinical trial study design for brain tumors. Patients undergo an initial phase 0 study component, with PK and PD endpoints assessed within 7 d of surgery. Positive PK and PD responses then qualify individual patients for subsequent therapeutic dosing as part of the phase 2 study component.

Although the phase 0 results inform go/no-go decisions regarding continued drug development, the phase 2 results provide added clinical and biological insight into drug resistance.

ROLE OF THE NEUROSURGICAL ONCOLOGIST

Many patients finish the surgical portion of treatment and then participate in adjuvant therapy clinical trials outside the scope of neurosurgical care. Neuro-oncology phase 0 studies are part of a larger surge in surgical trials proliferating within neurosurgery. Although interventional radiologists are able to allow safe access to tumor samples at various time points in non-CNS cancer studies, neuro-oncology tissue-based studies require a specific partnership with a neurosurgical specialist. Phase 0 strategies align the clinical and investigational teams from the start by initiating the investigation in the perioperative period. The neurosurgical oncologist, therefore, is a key component of the study design, patient accrual, and surgical phases. For the aspiring neurosurgical trialist, initiation of a phase 0 study begins with neuro-oncology collaboration and typically includes careful coordination with a brain tumor biologist, PK specialist, and other clinical trials infrastructure. Understanding the clinical and basic science trial elements is requisite for all team members and an essential element for the neurosurgeon.

In phase 0 studies, operative stringency and coordination across disciplines are essential for the study to gain any data of sufficient quality. Initially, the neurosurgical oncologist is critical for patient selection and study consent. For all phase 0 studies, a critical first step in patient selection is an assessment of tumor operability. This determination must account for the timing of the planned surgery. Unlike conventional clinical trials, brain tumor phase 0 studies require a substantial lead-in time prior to tumor resection. Molecular entry criteria are routine in phase 0 studies and typically demand 1 to 2 wk of testing a patient’s archived tumor tissue. Thus, eligible patients must be clinically stable, and the neurosurgical oncologist must assess the safety of timing an indicated operation to allow for trial pretesting and pretreatment.

During surgical operations, the operating room staff must carefully coordinate with the neurosurgical team to adhere to stringent protocols for time-sensitive tissue collection. PK analyses of phase 0 study drugs are predicated on timely acquisition of blood, CSF, and tumor tissue. In contrast to non-CNS phase 0 studies where tissue is often accessed with an outpatient needle biopsy, phase 0 studies for brain tumor patients include a craniotomy. Therefore, the feasibility of the study’s sample collection parameters relies heavily on operating room logistics and surgical timing. Phase 0 study patients present logistical challenges for the neurosurgical oncologist, and the key to overcoming those challenges is found in deliberate coordination with anesthesiologists, nurses, and surgical technologists among other operating room personnel in addition to case scheduling staff to mitigate potential delays common to the operating room.

Beyond enabling tissue acquisition, a neurosurgeon-neuroscientist should be facile in interacting with the preclinical and clinical datasets that emerge from phase 0 studies. In particular, the neurosurgical perspective should be incorporated into assessing the impact of samples bias and tumor heterogeneity when analyzing study results. The cumulative weight of the perioperative, intraoperative, and data analysis responsibilities handled by the neurosurgical oncologist makes this person a critical member of any phase 0 clinical trials team.

CONCLUSION

The phase 0 clinical trial mechanism originally proposed by the FDA was conceived with the general drug development community in mind. Brain tumor drug development, however, poses unique study limitations due to the absence of predictive animal models, the significant risks of tumor acquisition, the unsuitability of microdosing, the challenge of the
BBB, and the potentially confounding effects of neurosurgical anesthesia. Adapting the phase 0 trial paradigm for neuro-oncology patients is an effective avenue to obtain direct evidence of drug delivery and target modulation. Specific modifications include the following: (1) abandoning microdosing in favor of a higher-dose regimen, (2) using archival tissue as a pretreatment control specimen, (3) incorporating CSF into PK and PD analyses, (4) adding a phase 2 component for patients with demonstrable PK and PD responses, and (5) integrating the neurosurgeon into the trial team.

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COMMENTS

T he authors present a very interesting and cogent educational review about the phase 0 clinical trial concept in order to advance central nervous system (CNS) drug testing and development. The many challenges discussed in this primer include the following: inadequate preclinical tumor models, tumor heterogeneity that may not be reflected in individual patient specimens, the absence of adequate control tissues, the paucity of reproducible, clinically relevant models for testing human blood-brain barrier drug penetration, and adequate tumor or pathology-localized pharmacokinetics and pharmacodynamics of therapeutic agents. Although possible solutions (ie, induced pluripotent stem cell human blood-brain barrier models, new imaging methods, and cerebrospinal fluid/serum/cellular sampling strategies) are being investigated to solve the above challenges, careful clinical testing in humans will always be required. This primer highlights the central roles of neurosurgical oncologists and human clinical validation in the translation of drugs/agents for clinical CNS therapeutic use. Advances in designing and implementing phase 0/2 clinical trials will serve to optimize and streamline CNS drug testing and appropriately emphasizes the involvement of neurosurgeons in the design and execution of these important clinical studies to catalyze a rapid, safe, and effective drug approval process, ultimately benefiting our patients.

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