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Journal
Neuro-oncology practice, 4(4)

ISSN
2054-2577

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Publication Date
2017-12-01

DOI
10.1093/nop/npw034

Peer reviewed

Neuro-Oncology Practice
4(4), 201–208, 2017 | doi:10.1093/nop/npw034 | Advance Access date 14 February 2017

Clinical trial endpoints for patients with gliomas

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Abstract

Malignant glioma represents a diverse set of molecularly heterogeneous diseases. Few therapeutic agents have been approved despite decades of clinical trials research and pre-clinical investigation. Attempts to refine neuroimaging criteria and recent discovery of the genomic profiles linking tumor subsets to survival outcomes have spurred discussion on a variety of new approaches in clinical trial design and relevant endpoints. Here we focus on those endpoints in clinical trial design for patients with primary glioma and related issues still to be resolved.

Key words

clinical trial | endpoints | glioma | Neuro-oncology

The field of neuro-oncology continues to face significant challenges in clinical trial design and approval of new treatments. A critical component of appropriately interpreting and translating trial results is the integrity of the trial's primary endpoints. Advances in neuroimaging and insights into the biology of primary gliomas, and their treatments, continue to impact trial design and interpretation of results. The relationship between response and survival endpoints continues to evolve and, as such, endpoints are not standardized across trials. Patients with central nervous system (CNS) malignancies are also surviving longer, bringing to light neurocognitive consequences and the impact on quality-of-life from treatments.

Here we highlight some of the benefits and challenges of several commonly used endpoints in clinical trials of primary brain tumors. We will also discuss evolving endpoints as they relate to the Response Assessment for Neuro-Oncology (RANO), as well as implementation of adaptive design and trials based on molecular profiling.

Overall Survival

Overall survival (OS) is the gold standard endpoint for large, phase 3 trials in oncology. Measuring OS has the advantage of being objective and is felt to be the most significant effect of an investigational treatment. However, OS as a primary endpoint has several challenges. To detect statistically significant differences, larger accruals and longer study durations are needed. This can increase trial budgets and delay reporting of results, which may be difficult to interpret in the context of newer therapies.[1] Additionally, a treatment's impact on survival may be diluted or confounded by efficacy of salvage therapy—such as radiation therapy for low-grade gliomas—which is often underreported in neuro-oncology trials.[1]

Single-arm, non-randomized, phase 2 trials are designed to detect a signal for efficacy and provide support for larger phase 3 trials. Designs of such trials use data from historic controls as comparators. However, as the field advances and outcomes improve, survival data from historic controls may no longer be relevant, leading to misinterpretation of trial results.[2] In addition, baseline characteristics—such as the status of molecular markers and extent of resection—may differ significantly between the trial population and historic control. This has motivated the field to consider modifications of phase 2 design to address these challenges. One method is to conduct randomized phase 2 trials to include a more contemporary control arm, though study durations may be longer and accrual more difficult.[2] Another method is to use prespecified, well-defined survival rates at 6, 9, or 12 months; while this may have the

advantage of shortening trial length, larger sample sizes are often required.[1]

Progression-free Survival

Progression-free survival (PFS) is defined as the time from study enrollment until one of the following events: 1) progression based on imaging; 2) progression based on neurologic exam; 3) increasing steroid use to control symptoms; or 4) death. PFS is often reported as either a median or percentage of patients alive and progression-free at a prespecified point in time, most often at 6 months (PFS-6). PFS is a widely used endpoint in phase 2 trials for high-grade gliomas. PFS-6, in particular, is considered a surrogate marker of OS.[3,4] This was demonstrated in the EORTC 26951 and RTOG 9402 trials, two large trials of radiation with or without chemotherapy in anaplastic oligodendrogliomas.[5,6] However, the PFS and OS failed to correlate in the RTOG 0825 and AvaGlio studies of radiation and temozolomide with or without bevacizumab in newly diagnosed glioblastoma. While there was improvement in median PFS, with a hazard ratio (HR) of 0.79 ($P = .007$) for RTOG 0825 and 0.64 ($P < .001$) for AvaGlio, there was no difference in OS, with a HR of 1.13 ($P = 0.21$) for RTOG 0825 and 0.99 ($P = 0.10$) for AvaGlio.[7,8] This highlights that bevacizumab, both up front and as a salvage therapy, makes PFS as a primary endpoint more difficult to interpret.

In the two phase 2 trials of bevacizumab that lead to its accelerated approval as a monotherapy for recurrent glioblastoma in the United States, PFS-6 rates were reported at 42%[9] and 29%.[10] The primary reason for accelerated approval, however, was based upon objective imaging response (compared to historical controls), rather than PFS or OS. There were no comparator arms in these trials. Bevacizumab's improvement of PFS in relapsed or newly diagnosed patients was not predictive of an improvement in OS in the newly diagnosed setting when put to the true test of a randomized phase 3 study. However, bevacizumab is now commonly used as the comparator arm for randomized phase 2 and 3 trials for recurrent glioblastoma. Recent trials using bevacizumab monotherapy as a control arm report PFS-6 as ranging from 11% to 20%, far lower than the studies leading to its approval by the Food and Drug Administration (FDA).[11–13] A possible explanation for this discrepancy is increasing recognition of pseudoprogression, post-radiation inflammatory changes that lead to increased contrast-enhancement and vasogenic edema, and often mistaken for early tumor progression and started on bevacizumab.[14,15] Pseudoprogression will often subside without intervention and has, in fact, been shown to correlate with improved outcomes (Figure 1).[14,15] Earlier trials of bevacizumab likely included these patients, therefore overestimating its effect on PFS. Modern clinical trials exclude enrollment of patients who are less than12 weeks from completing radiation, or require histologic confirmation of progression, to minimize this confounding factor.

Despite its limitations, PFS as a primary endpoint is particularly useful in the setting of low-grade gliomas or anaplastic gliomas. These patients may live more than a

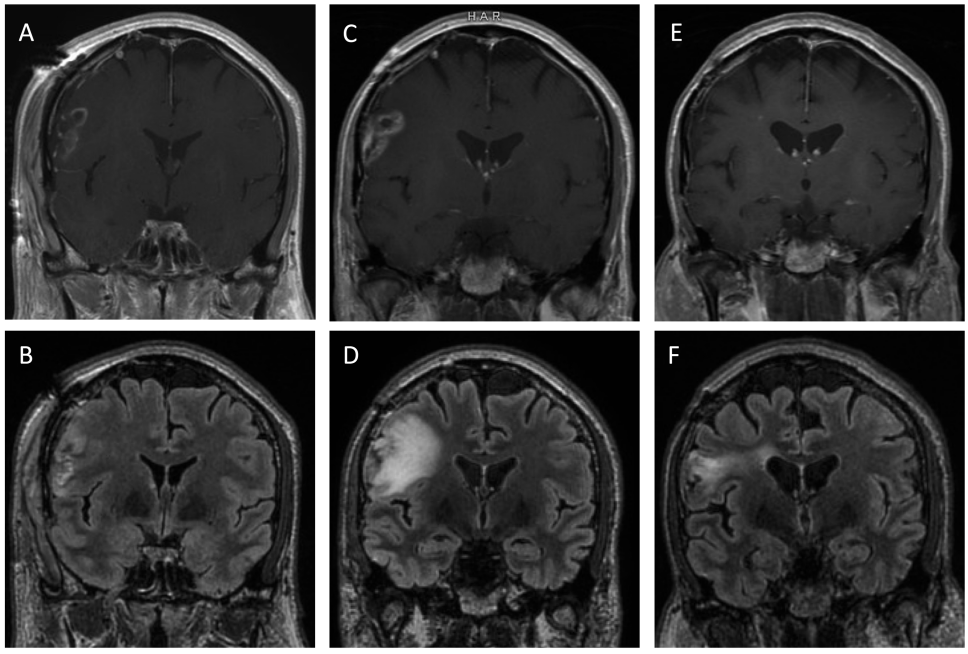

Fig. 1 Pseudoprogression observed in a patient with right frontal, MGMT-methylated glioblastoma. Postoperative coronal MRI demonstrating subtotal resection of right frontal glioblastoma by (A) T1 postcontrast and (B) fluid attenuation inversion recovery (FLAIR). MRI 3 months after completion of radiation, demonstrating (C) thickened nodular enhancement on T1 postcontrast imaging and (D) increased edema on FLAIR. The patient was asymptomatic and completed 1 year of adjuvant temozolomide. MRI at 22 months after completion of radiation and 10 months after completing 1 year of adjuvant temozolomide, demonstrating (E) resolution of enhancement and (F) resolution of edema with residual gliotic changes.

decade after diagnosis, thereby making trials with OS as the primary endpoint difficult. There is also suggestion that PFS may be superior to OS in the setting of these diagnoses, as it is independent from effects of salvage treatments such as radiation.[16] In this scenario, PFS allows for smaller sample size and shorter trials for determining efficacy.[17] The EORTC 26951 and RTOG 9402 trials of radiation with or without chemotherapy in anaplastic oligodendroglioma demonstrated that PFS correlated with OS in these patients.[5,6]

Radiographic Endpoints

Radiographic response rates in neuro-oncology have evolved significantly over the last few decades. In most malignancies, radiographic responses can be measured in a single dimension by the RECIST (Response Evaluation Criteria in Solid Tumors) criteria. Brain tumors, however, are more irregularly shaped and complex, necessitating more complex measurements to reflect treatment response.[18,19] The Macdonald criteria[20] were proposed in the 1990s and use two-dimensional measurements of the contrast-enhanced MRI, along with clinical status and dexamethasone dose. The MacDonald criteria were adapted to the RANO (Response Assessment in Neuro-Oncology) criteria in 2010, in response to bevacizumab's effect on decreasing contrast enhancement and recognition of the importance of the T2 and FLAIR sequences as indicative of infiltrative tumor.[21]

Overall radiographic response (ORR), or the change in the two-dimensional measurements of the enhancing mass, is an attractive endpoint in its independence from effects of salvage therapy. However, it can both overestimate and underestimate a therapeutic effect, as highlighted by the phenomenon of pseudoresponse and pseudoprogression.[22,23] The recognition of these entities has posed significant challenges for implementing ORR as an endpoint.

Bevacizumab received accelerated FDA approval for recurrent glioblastoma[24] based on ORR rates of approximately 30%,[9,10] though subsequent trials of bevacizumab in newly diagnosed glioblastoma failed to demonstrate improvement on overall survival.[8,25]

Pseudoresponse refers to the impact of vascular endothelial growth factor (VEGF) inhibitors on radiographic changes. VEGF inhibitors, such as bevacizumab, decrease permeability of tumor vasculature, leading to rapid reduction in gadolinium contrast extravasation. Though this response may be dramatic and significantly improve neurologic symptoms by reducing vasogenic edema, the tumor bulk itself may be unchanged. Recognition of this phenomenon and attention to non-enhancing sequences such as T2, fluid attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI) is imperative to assessing response. In recognition of pseudoresponse, the RANO criteria incorporated FLAIR changes into the overall assessment.[21]

Pseudoprogression, as described above, is the product of inflammation and blood-brain barrier disruption from radiation treatment and is characterized by increased contrast enhancement, vasogenic edema, and potentially worsened neurologic function. Pseudoprogression is expected in 20% to 30% of patients within 3 months of completing treatment and associated chemotherapy.[21] This would be defined as progressive disease based on the MacDonald and RANO criteria, which risks underestimating the response to radiation and temozolomide and radiographically defining progression too early.[14,15] Because of this imaging confounder, most clinical trials done at the time of relapse only allow enrollment after 3 months from the end of radiotherapy, unless the tumor is surgically proven to be progression, or an appearance of a new lesion outside of the radiation treatment plan is detected. Even with this inclusion rule, there are clear examples (surgically proven) of pseudoprogression beyond 3 months due to the late effect of radiation. Because many patients never undergo additional surgery, one cannot be 100% certain when progression really occurs. Imaging remains a surrogate of disease activity, and not a direct measure of tumor status.

As neuro-oncology enters a new phase of testing immunotherapies, experiences with bevacizumab have inspired the proactive definition of response assessments related to immunotherapy. For example, iRANO is an effort for incorporating immune-related responses into the standard RANO criteria, defining progressive disease as the presence of persistent radiographic changes. The intention is to allow patients with stable neurologic exams to remain on treatment 1 to 2 months longer after a change in enhancement and T-2 FLAIR, which may really represent localized immune response similar to pseudoprogression, in order to confirm radiographic evidence of progression or stable, responding disease.[26]

ORR is not a proven surrogate marker for PFS and OS. Nor does it adequately reflect the significant impact of stable, nonprogressive disease achieved by cytostatic treatments, which can be very clinically meaningful.[17] Interpretation of neuroimaging is also subjective and dependent on expertise. Therefore, when ORR is to be included as an endpoint, independent central review is imperative.[17]

Quality of Life and Neurocognitive Function

Included within the definition of progressive disease and within the RANO assessment, is the status of neurologic function. However, objective tools for measuring neurologic function and standardization across trials are lacking. The Neurologic Assessment in Neuro-Oncology (NANO) was devised to address this issue and provides a quantitative neurologic exam and evaluation of response to treatment.[27] This has been incorporated in ongoing clinical trials for malignant gliomas.

With improvements in treatments and better understanding of molecular markers associated with improved prognoses, subsets of patients with gliomas are living longer. This highlights the importance of recognizing the effects of treatment not only on survival, but also on cognition and health-related quality of life (HRQOL). HRQOL incorporates how the disease and treatment influence the patient's physical, psychological, and social functioning.[28] The call to incorporate HRQOL and cognition measures in

trials for patients with brain tumors is complicated by the primary disease's impact on cognition and HRQOL.[29,30]

Several instruments have been developed and validated to assess patient-reported outcomes of HRQOL specific to brain tumors. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire—Brain Cancer Module (EORTC QLQ-BN20) is a 20-item questionnaire that was adapted from the larger EORTC QLQ-C30 to be specific to brain tumor patients and focuses on symptoms.[31] The MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT)[32] and the Functional Assessment of Cancer Therapy-Brain (FACT-Br)[33] are additional standardized tools, which focus more on psychosocial impacts.[29,30] These instruments were used as secondary endpoints in several recently published pivotal trials of bevacizumab in newly diagnosed glioblastoma.[34]

Scores from the Mini-Mental State Examination (MMSE) and performance status scales such as Karnofsky Performance Status and Easter Cooperative Oncology Group Performance Status capture significant clinical data, though should not be substituted for HRQOL outcomes.[29] Additionally, the MMSE exam is a crude tool and sensitive only for identifying severe impairment.[35]

Assessing the neurocognitive effects from treatment in patients with brain tumors is complex, given the effect of tumor progression and location on cognition. Neurocognitive status does correlate with clinical status, with stabilization providing a direct measure of clinical benefit. Neurocognitive batteries should be brief, sensitive, standardized, and easily repeatable.[36] Currently, the Hopkins Verbal Learning Test, Controlled Oral Word Association, and Trail Making Test Parts A and B comprise the core of testing and can be completed in 20 minutes.[36] It has been proposed that neurocognitive outcomes should be included as a co-primary endpoint, along with radiographic and neurologic endpoints.[36]

Molecularly Informed Trials

Molecularly informed trials include the use of biomarkers. A prognostic-only molecular marker can stratify patients into groups with distinct outcomes, independent of any specific treatment. Predictive markers define patients who are more likely to respond to a specific treatment. Some makers can be both prognostic and predictive. In most types of glioma, age, an easy-to-assess biomarker, is highly prognostic (younger patients live longer than older patients). Promoter methylation of the *MGMT* gene or mutation in the *IDH-1 R132H* gene defines a subset of glioblastoma patients with significantly longer survival expectation, and are considered prognostic biomarkers.[37,38] Recent evidence suggests that knowledge of chromosome 1p/19q deletion, *IDH-1* mutation, and *TERT* mutation can effectively define prognosis in high-grade and low-grade glioma.[39] Thus, all of these factors must be considered in clinical trial design, and are equally important in analyzing results of therapeutic interventions. In trials for which OS is a primary endpoint, prognostic biomarkers must be taken into account.

In addition to prognostic biomarkers, some evidence suggests that the presence of key molecular alterations may be predictive of treatment response. Promoter methylation of the *MGMT* gene, a prognostic biomarker, is also predictive of longer duration of response in patients with glioblastoma treated with radiation and temozolomide, which are DNA-damaging agents. Deletions of regions of chromosomes 1p and 19q are also now felt to be predictive of response (measured as delay in progression) in patients with oligodendroglioma when cytotoxic chemotherapy is added to radiotherapy. Unfortunately, other than these few examples of prognostic and predictive biomarkers in glioma, few molecular markers are validated as being predictive of response, either measured as OS, PFS, or imaging response. The dilemma of course is that standard treatment options are few, most patients ultimately succumb to their disease, and historically clinical trials that have not selected patients based upon biology have been negative. Indeed, positive outcomes in early phase studies done at the time of relapse have not subsequently been shown to be effective in controlled randomized trials at the time of initial diagnosis.

Because of the marked heterogeneity of malignant gliomas, they are no longer considered a single disease entity, and treatment using one agent in unselected patients has proven ineffective as a therapeutic strategy. Advances in molecular profiling using deep sequencing of DNA and RNA, with results now typically available within days or weeks, allows clinicians to make choices based upon individual patient genomic signatures. Basket or bucket studies rely upon the use of enrichment strategies using tissue-based biomarkers to select therapies. Basket studies use molecular information to target a specific mutation that might be found in a number of different cancers. In this strategy, the target (genotype), rather than the disease (phenotype), is hypothesized to be more important. These studies are frequently done in rare cancers. For instance, a mutation of BRAF may be detected in melanoma, glioma, or colon cancer. Basket trials using targeted agents against this mutation will allow any cancer type to enroll. The NCI-supported MATCH trial is an example of a study using this strategy. On the other hand, bucket studies tend to use genomic information within a specific disease for therapy selection. In this scenario, all eligible patients with malignant glioma would have profiling done, and one of several, predefined drug treatments would be assigned based upon the biomarkers of interest detected in subsets of patients. Biomarkers used in these types of interventional studies are typically hypothesized to be predictive, as opposed to prognostic. The endpoint of many basket trials is response or PFS, with the goal to detect some signal of efficacy within subsets of patients. Positive studies would then lead to randomized controlled trials with OS as an endpoint. One criticism of the use of basket studies for CNS tumors is the appropriate concern that most therapeutic agents are not designed to cross the blood-brain or blood-tumor barriers. A specific inhibitor that might be effective against a specific mutation in the lung may not have any impact in a brain tumor patient simply because of the exclusion of that agent from the brain.

Newer clinical trials have begun to take into account all of the information available in order to select therapies

linked to the specific biology of the disease. These trials are often exploratory in that the biomarkers chosen, while integral to the trial, have typically not been fully validated as predictive markers in glioma. Preliminary evidence may suggest that the presence of a particular mutation in a gene will likely result in alteration of critical pathways necessary for tumor maintenance. This evidence may be based upon preclinical models or anecdotal responses seen in a small number of patients treated with specific agents linked to specific mutations in uncontrolled trials. Patients with a unique mutation ($BRAF^{V600E}$) in their tumor may respond to one of several available specific inhibitors of that mutation. High ORR has been shown in malignant melanoma patients who harbor this mutation. This particular mutation is rare in adult glioma, and more common in pediatric low-grade tumors. Unfortunately, early objective responses in glioma may be short, or some patients with the mutation will not have any evidence of benefit. The molecular underpinnings of the pathway in glioma are different than in melanoma, particularly resistance mechanisms, and are still poorly understood. The selection criteria defining specifically which patients are more likely to benefit are still being developed. This example highlights the fact that similar mutations seen in one type of cancer may not predict responses in patients who have a different cancer, even when treated with the same targeted therapeutic agent.

There are a number of methodologies used to assess tumor biology, including RNA expression, copy number data, whole-exome or whole-genome mutation studies, or single-mutation genotyping. Molecular "signatures" are often employed, combining both RNA and DNA alterations. Biomarkers used for selection are tested for in a Clinical Laboratory Improvement Amendment (CLIA) certified laboratory. Concise, analytic validation of these various methods is critical towards ultimate qualification of the biomarker(s) used for selection of therapeutic agents. Precision medicine mandates that the biomarker is reliable, validated, and predictive. The choice of biomarker is often the most important factor to be considered when these types of trials are being designed.

Objective response or progression-free intervals are often used as endpoints to assess benefit, particularly in biomarker-driven trials. As mentioned earlier, PFS may not necessarily be predictive of OS. Objective response may not be predictive either of PFS or OS, and is confounded by the surrogate nature of MR-based imaging in glioma. Thus, one has to consider what signal is important, and plan for subsequent studies to either validate any observed benefit, even if transient, to confirm a clinically meaningful benefit (eg, improvement in OS or quality of life). Hitting a molecularly defined target, and altering biology, may be an important first step in drug development, but may not necessarily result in improvement in survival. Phase 0 studies are often used in neuro-oncology to ensure adequate drug exposure within the tumor compartment, as well as modulation of the genomic target. Knowing why a treatment strategy fails is equally important, particularly when testing a hypothesis. Repeat surgeries to obtain posttreatment tumor tissue, though very helpful in this regard, are unfortunately rarely done in patients with malignant glioma. Thus, one frequently has to rely on surrogate markers, including imaging, toxicity, or liquid biomarkers in blood. As mentioned earlier some therapies will impact the determination of objective response seen with imaging (eg, antiangiogenic agents) or progression-free intervals.

Whether to use a concurrent control arm in these studies is also important. Single-arm studies specifically using a predefined biologically driven approach will of necessity rely on historical data when assessing success or failure, often data from trials that had not categorized patients based upon the molecular subset being tested. A single-arm, molecularly enriched study might use objective response as the first signal of success, rather than PFS, since the natural history and rate of tumor growth of subgroups defined by the biomarker may not be known. In addition, if the trial only treats patients with a specific genomic profile/marker, using a specific inhibitor, information about the drug in biomarker-negative patients will be unknown, potentially excluding an effective drug for those patients. Allowing biomarker-negative patients into trials would be important for this reason. Early stopping rules for futility are typically incorporated in the design of such studies. A randomized phase 2 trial enriched for a molecular subgroup, but which treats patients either with a targeted agent or a standard agent, is another approach, and addresses the question of biomarker–treatment interaction. A "randomize-all" strategy could allow patient assignment of a targeted agent to biomarker-positive and negative patients, and have a concurrent control arm, with equal balance in each arm. This type of study may offer the best information regarding the hypothesized effect of target/drug characteristics. A limitation of this approach is the larger sample size needed to detect significant differences in outcome. One approach to minimizing sample size would be to employ an adaptive strategy, allowing adjustments in assignments over time as response information is gathered.

The structure of an ideal bucket trial in glioma would require acquisition of tumor tissue just prior to treatment, using a predetermined profiling strategy to select both target(s) and drug(s). One could choose to drug one target or multiple targets if the data supports multiagent strategies. Patient eligibility would require knowledge of the presence or absence of a specific biomarker and the availability of a specific targeted agent. Not all patients will be eligible for such studies. Those that enroll, however, should be as homogeneous as possible for known prognostic factors. If historical controls are used to assess success or failure, those studies should be carefully chosen to ensure some degree of similarity both in terms of eligible patients and similar, if not identical, biomarker knowledge. Controlled trials are valuable and should be considered if possible, when the natural history is not known relative to the biomarker of interest. Repeat biopsies at the time of progression would allow assessment of potential mechanisms of resistance. Because of the issue of altered blood-brain barrier and blood-tumor barrier and potential lack of adequate exposure of biologically relevant drug concentrations, one would want to choose drugs that have a greater likelihood of CNS penetration into regions of infiltrating tumor. In the best of worlds, one would first want to biopsy a tumor, determine the genomic profile, choose a drug of interest, then give that drug at a dose and schedule that would optimize target modulation just prior to a planned

second surgery to assess both the pharmacokinetic and pharmacodynamic aspects of the agent. Having the knowledge that a drug hit its target and had a biological effect would clearly strengthen any clinical observation that followed with more prolonged treatment. Phase 0 trials are designed to give this type of information, and to screen for drugs that would ultimately be futile for continued testing. The number of patients needed for that type of study is small and minimizes exposure to agents that will ultimately be unsuccessful in larger patient populations. Drugs that have good performance proven in a Phase 0 study should be prioritized for Bucket trials that test efficacy.

Adaptive Design

The FDA defines an adaptive design clinical study as "a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study."[40] That is, adaptive trials differ from standard trials in that they seek to answer multiple questions in one trial and do so by modifying the course of the trial as data accumulates.

An advantage of multiarm, adaptive design clinical trials is that by combining many questions at once, one trial may identify the optimal patient population, drug dose, and combinations of therapies, providing more information in a shorter time period than performing several subsequent traditional trials. For example, the combinations of phase 1-2 or phase 2-3 trials serve to answer many questions simultaneously and shorten the time for drug development.

There are multiple ways to accommodate adaptive settings in clinical trials, which can be used concurrently or individually. Such examples include: seamless transition from phase 1 to 2 or phase 2 to 3 in a single trial; altering the proportion of patients randomized to each arm; adding arms or doses; adaptively assigning doses; altering the accrual rate; and stopping early for superiority or futility or stopping late for extending accrual.

An important consideration in designing an adaptive clinical trial is the clinical endpoint. As described above, in oncology, OS is the gold standard. However, OS has to be assessed over an elongated period of time. In an adaptive trial this means few patients can be evaluated for OS in the initial stages of the trial, providing little information and making it difficult to modify the trial's course. Therefore, surrogate endpoints such as PFS-6, imaging, and/or patient performance status could be used. Nevertheless, the inference of the trial should be based on OS.[41]

Adaptive trials can be either Bayesian or frequentist in statistical nature. The differences between the 2 are beyond the scope of this article and the interested reader is directed to several articles by Donald Berry for a thorough review.[42–44] Regardless of which approach, the FDA guidelines require that all adaptations be detailed in the protocol so that the type I and II error and power can be specified. To do so, extensive computer simulations are necessary to estimate the sample size, trial duration, drug doses/amounts, and number of time points at which adaptations can occur. An additional consideration that needs to be detailed is how the data will be warehoused and continuously accessed for monitoring potential modifications of the trial.

There are many options for implementing adaptive trials in glioma. For newly diagnosed glioblastoma patients, standard of care (radiation and temozolomide) could be combined with other therapeutics in multiple arms or patients could be randomized to therapeutics on different treatment arms following radiation and temozolomide.[45] In both cases, PFS-6 could be used for randomization probabilities and evaluated as the trial progressed. For patients with recurrent glioblastoma, given the lack of current standard of care, 2 options would be to have multiple arms where each arm included bevacizumab and an additional therapeutic or multiple arms where 1 arm included bevacizumab and the others were potential substitutes for bevacizumab. Again, PFS-6 could be used for adaptation and evaluated as the trial progressed.

Conclusions

In conclusion, endpoints for clinical trials in neuro-oncology continue to evolve. While OS remains the gold standard, there are benefits to exploring alternative endpoints. Advances in imaging and increasing recognition of treatment effects on MRI are strengthening the use of radiographic response as endpoints. As neurocognitive testing and quality-of-life metrics become more standardized, they too will become more useful and generalizable trial endpoints. Novel trial designs, including Basket and Bucket studies, using targeted agents based on genomic signature and not on cancer type, are also emerging in neuro-oncology. Additionally, adaptive trial design that focuses on addressing several questions within one trial is widely being incorporated in new clinical trials. This arsenal of evolving endpoints and novel trial designs will accelerate the identification of effective treatments for this patient population.

Conflict of interest statement. The authors have no conflicts of interest to disclose and no funding was involved in the preparation of this manuscript.

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