Use of External Control Cohorts in Pediatric Brain Tumor Clinical Trials

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Introduction

CNS tumors are the most common source of cancer-related death in children and are heterogeneous with varied molecular pathogeneses, resulting in a small population of over 70 subtypes.[1-6] They are also heterogeneous with respect to outcomes, with some having very poor survival rates because of lack of effective therapies.[6-11] Prospective randomized clinical trials are often infeasible because of the rarity of the disease and the unwillingness of parents and physicians to enroll on trials that randomly assign patients to ineffective control arms. In such scenarios, data from other clinical trials and real-world data may be used to construct high-quality patient-level data sets that serve as external control arms to evaluate time-to-event end points such as event-free survival and overall survival. The National Brain Tumor Society convened a Research Roundtable of clinicians, statisticians, industry representatives, regulatory officials, and patient/caregiver representatives to discuss considerations for using externally controlled designs in pediatric brain tumor clinical trials. The goal of the meeting was to develop recommendations for the successful implementation of external controls and to work with industry and regulatory partners to guide the development of appropriate data sets and trial designs that could support registration studies.

Patient Perspectives

The treatment options for children with brain tumors are limited, and more clinical trials, especially those that optimize the use of novel designs and limit the placement of patients on ineffective control arms, are essential for advancing treatments. The concept of data sharing is of particular importance to pediatric patients with brain tumor and their families. Parents continually stress the need to eliminate barriers to sharing patient data among research institutions to facilitate use in clinical trials. The use of external control arms should be pursued, where feasible, to ensure that patient data are used and to appropriately encourage parents and patients to enroll in well-designed clinical trials.

Regulatory Perspectives and Definitions

The US Food and Drug Administration (FDA) recommends a randomized trial in all circumstances when feasible, particularly for diseases in which imaging-based end points are problematic.[12] In rare cases, the use of an external control arm may be considered where random assignment may be infeasible, unethical, or impractical. Appropriateness of a study design incorporating external controls is contingent on the ability of the data to reliably demonstrate and isolate the treatment effect. External control arm suitability is reliant on many factors that require careful evaluation before study initiation including, but not limited to, data source, comparability of patient populations, contemporaneity, and completeness of the data.[13] To meet FDA's requirement for substantial evidence of efficacy, additional confirmatory evidence would need to be provided to support a single externally controlled trial. This would typically be in the form of additional supportive clinical data in addition to strong nonclinical data supporting the mechanism of action.

The extent to which data can be used to support an external control is largely dependent on the data source. Sources may comprise real-world data (eg, data from electronic health records, administrative claims data, registries, patient-generated data), previous clinical trial data, or literature-based data. Sources that do not contain patient-level data are rarely suitable for regulatory purposes.

In all cases, the use of an external control arm is typically the exception rather than the rule, and trial sponsors are strongly encouraged to meet with FDA by reaching out to the relevant review division as early as possible to ensure alignment on the trial objective, study feasibility, protocol, statistical analysis plan, and applicability for regulatory decision making before study initiation[14] (eg, pre-IND meeting, type C or type D meeting depending on the stages of development).

Industry Perspectives

Industry partners face many financial issues regarding developing new agents for children with brain tumors. Given the small pediatric population, the economics of expensive clinical trials are often unjustified, especially since few additional regulatory incentives are available to support these costs. Although industry studies are now required to meet regulatory requirements, including a pediatric investigation plan for the European Medicines Agency and a pediatric study plan for the FDA, they tend to focus on phase I and pilot phase II trials. They are usually not designed to gain approval for a pediatric indication. For smaller biotechnology companies with limited resources, where some of the most significant innovation occurs, the cost and duration of randomized trials become further deterrents to performing such studies, leaving clinicians with hints of activity but needing more comprehensive assessments to make genuinely informed treatment decisions. Although a randomized trial is the gold standard, novel approaches, such as inclusion of external controls that still accurately define the benefit of a new treatment, may be more efficient for pediatric CNS tumors and could lead to improved assessment and hopefully actual registration of novel therapies for this poor prognosis, high unmet need, and underserved patient population.

Data and Database Infrastructure

Data for external control cohorts can come from a variety of sources including clinical trials and real-world data. When using an external control cohort, it is important that the patients in the cohort are the same or very similar to those in the trial with regards to eligibility criteria and clinical and demographic characteristics that may affect prognosis or response to therapy. Care should be taken to ensure comparability of patient characteristics, disease severity, geography, outcome measures, and cancer-directed and supportive therapies before and subsequent to the treatment period under investigation. This is critical to assure that any improvement in outcome is due to the investigational therapy rather than a confounding factor. Concurrent controls are preferred as they include a patient population treated during the same or similar period, increasing the likelihood of a similar standard of care (SOC). The variables often required for a well-annotated data source include but are not limited to detailed diagnosis, disease evaluation criteria, imaging, patient demographic and clinical characteristics, clear treatment history, and the date and type of recurrences. Assessment for variables that require interpretation such as eligibility and disease response may not be consistently evaluated across data sets, and as such central review of real-world data is recommended whenever feasible.

Maximizing completeness of data is imperative as interpretation of study results can be affected by missing data for key clinical covariates emphasizing the need for data standards and methods of data collection and integration. Unfortunately, some data sources may not contain the necessary information to reasonably assess or assure comparability and may not be suitable for use as an external control cohort.

Data infrastructure has been a long-standing central challenge for developing the necessary resources to support the implementation of external controls. The pediatric brain tumor community has had several efforts coordinating and integrating such data, laying the foundation for National Institutes of Health–sponsored national initiatives, including Gabriella Miller Kids First Program and the National Cancer Institute's Childhood Cancer Data Initiative. Additional efforts are underway to define a CNS common data model and associated data dictionary, mapping terminologies and variables being used across The Children's Oncology Group, the Pediatric Neuro-Oncology Consortium, the European Society for Paediatric Oncology, the International Diffuse Intrinsic Pontine Glioma/Diffuse Midline Glioma Registry, the Rare Brain Tumor Consortium, and the Children's Brain Tumor Network.[15] Although such efforts have significantly advanced the cross-institutional control cohort data potential, there is still a significant need for resource development.

Statistical Perspectives

Randomized controlled trials are the gold standard for establishing efficacy because random assignment removes confounding by both known and unknown factors. When a randomized trial is not feasible, external control arms can be viable for estimating comparative treatment effects by augmenting a concurrent control group or creating a standalone control group. Other ways to use external controls include delineating the natural history of a disease, estimating the null hypothesis for a single-arm trial,[16,17] and making early futility-stopping decisions.[18] The quality of the data source for external controls determines how and to what extent the external controls can contribute to the design of a clinical trial.

Several ways exist to augment a concurrent control group with external data. If random assignment is feasible and a SOC treatment is available, most patients can be randomly assigned to the experimental treatment arm and a minority to the SOC therapy concurrent control arm with the intent to augment the control arm with external data (eg, hybrid design).[19-21] Once accrued, the patients in the concurrent control arm can be compared with the external control patients to verify consistency. One approach is to assess the similarity in the outcome distribution between the concurrent and external control patients. A Cox proportional hazards model including a study effect (for the concurrent *v* external control sets) is adjusted for prognostic patient characteristics. After a predetermined number of patients are enrolled, the similarity in outcome distribution is assessed. If the absolute value of the standardized study effect (ie, absolute log hazard ratio/SE of the log hazard ratio) does not exceed 1.64, the 95th percentile of a standard normal distribution, the conditional survival distributions will be considered equivalent. Once confirmed, borrowing for combined assessment can be allowed. Alternatively, novel Bayesian statistical approaches for dynamic borrowing between the external and concurrent control arms allow the data, not the investigator, to choose the borrowing level without compromising the estimates' precision.[22]

When random assignment is not feasible, all enrolled patients receive experimental treatment, and efficacy is compared with an external control cohort. To demonstrate treatment efficacy using an external control arm, the experimental and external control arms must be similar in temporality, balanced in clinical factors, and include objectively and consistently measured primary end points again highlighting the need for reliable and comprehensive clinical data.[17] It is essential that the external data include extended follow-up with as few censored patients as feasible. The external control cohort may incorporate more than one data source, and if external data from different sources produce similar results, this may increase the confidence in the reliability of the comparative estimates.[22]

Even with carefully annotated data, investigators must use analytical methods to address bias and confounding. Methods to control selection bias and confounding include restricting the external control data to a matching subgroup, building scores to mathematically balance factors (eg, propensity scores and inverse probability weighting), and incorporating weights to control time-varying confounding (eg, marginal structural models).[16,23,24] However, analytical methods can only address some bias/confounding and require extensive planning and justification. For the latter, in sensitivity analyses, the investigator should compare multiple methods to verify concordant results and illustrate the robustness of the chosen analytic approach.[17] An important parameter in such assessments is the choice of the effect size.

Generally, the proposed effect size must be larger in an externally controlled trial than in a randomized trial to minimize the likelihood that an observed result is not due to uncontrolled factors. There needs to be consensus about the degree of the observed improvement in an outcome that would convince stakeholders that the therapy is effective. One way to assist in this is to incorporate sensitivity analyses as part of the design efforts using the control data intended for comparison to ensure that the proposed effect size is not expected by chance alone on the basis of the variability in the historical data. The requirement for a larger effect size will inherently preclude detection of small improvements in measured outcomes and must be considered when choosing a study design.

It is crucial to incorporate futility rules when using external controls to ensure that the trial stops as early as possible if the new treatment approach is unlikely to meet the planned efficacy threshold to minimize harm and to ensure that other trials can be conducted in rare patient populations. We recommend futility rules that ensure at least 50% probability of stopping before accrual completion if the therapy has efficacy very similar to the external control cohort. Conversely, if there is a signal of effect/efficacy at the interim point, the trial is typically not stopped to generate as much convincing efficacy data as possible supplemented by complete toxicity and tolerability information. Recent developments in the statistical literature include efficient methodologies in calculating sample sizes for such designs and provide coherent strategies for interim analyses in the context of external controls.[25]

Discussion, Next Steps, and Conclusions

Despite their rarity, pediatric brain tumors have a tremendous impact on the population, responsible for an estimated 48,000 years of potential life lost.[26] While we should continue to advocate for randomized controlled trials where feasible, using external controls may improve the feasibility of conducting efficacy studies in rare cohorts in a reasonable time frame. Successful externally controlled trials require well-annotated, validated data from fit-for-purpose sources, and early engagement with industry and regulatory partners is imperative to ensure that trials are rigorously designed to support regulatory approval.

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REFERENCES

1. Ho B, Johann PD, Grabovska Y, et al: Molecular subgrouping of atypical teratoid/rhabdoid tumors—A reinvestigation and current consensus. Neuro Oncol 22:613-624, 2020
2. Louis DN, Perry A, Wesseling P, et al: The 2021 WHO Classification of Tumors of the Central Nervous System: A summary. Neuro Oncol 23:1231-1251, 2021
3. Lassaletta A, Zapotocky M, Mistry M, et al: Therapeutic and prognostic implications of BRAF V600E in pediatric low-grade gliomas. J Clin Oncol 35:2934-2941, 2017
4. Pajtler KW, Mack SC, Ramaswamy V, et al: The current consensus on the clinical management of intracranial ependymoma and its distinct molecular variants. Acta Neuropathol 133:5-12, 2017
5. Braunstein S, Raleigh D, Bindra R, et al: Pediatric high-grade glioma: Current molecular landscape and therapeutic approaches. J Neurooncol 134:541-549, 2017
6. Ostrom QT, Price M, Ryan K, et al: CBTRUS statistical report: Pediatric Brain Tumor Foundation Childhood and Adolescent Primary Brain and Other Central Nervous System Tumors diagnosed in the United States in 2014-2018. Neuro Oncol 24:iii1-iii38, 2022 (suppl 3)
7. Hargrave D, Bartels U, Bouffet E: Diffuse brainstem glioma in children: Critical review of clinical trials. Lancet Oncol 7:241-248, 2006
8. Bradley KA, Zhou T, McNall-Knapp RY, et al: Motexafin-gadolinium and involved field radiation therapy for intrinsic pontine glioma of childhood: A Children's Oncology Group Phase 2 study. Int J Radiat Oncol Biol Phys 85:e55-e60, 2013
9. Su JM, Kilburn LB, Mansur DB, et al: Phase I/II trial of vorinostat and radiation and maintenance vorinostat in children with diffuse intrinsic pontine glioma: A Children's Oncology Group report. Neuro Oncol 24:655-664, 2022
10. Kilburn LB, Kocak M, Schaedeli Stark F, et al: Phase I trial of capecitabine rapidly disintegrating tablets and concomitant radiation therapy in children with newly diagnosed brainstem gliomas and high-grade gliomas. Neuro Oncol 15:759-766, 2013
11. Baxter PA, Su JM, Onar-Thomas A, et al: A phase I/II study of veliparib (ABT-888) with radiation and temozolomide in newly diagnosed diffuse pontine glioma: A Pediatric Brain Tumor Consortium study. Neuro Oncol 22:875-885, 2020
12. FDA Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, Draft Guidance for Industry. Rockville, MD, US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Oncology Center of Excellence (OCE), 2019
13. FDA Guidance for Industry: Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products: Guidance for Industry. Rockville, MD, US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Oncology Center of Excellence (OCE), 2023
14. FDA Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicant of PDUFA Products. Rockville, MD, US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), 2017
15. Plana A, Furner B, PaleseDussault MN, et al: Pediatric cancer data commons: Federating and democratizing data for childhood cancer research. JCO Clin Cancer Inform 10.1200/CCI.21.00075
16. Ventz S, Lai A, Cloughesy TF, et al: Design and evaluation of an external control arm using prior clinical trials and real-world data. Clin Cancer Res 25:4993-5001, 2019
17. Thorlund K, Dron L, Park JJH, et al: Synthetic and external controls in clinical trials—A primer for researchers. Clin Epidemiol 12:457-467, 2020
18. Ventz S, Comment L, Louv B, et al: The use of external control data for predictions and futility interim analyses in clinical trials. Neuro Oncol 24:247-256, 2022
19. Ventz S, Lai A, Cloughesy TF, et al: Design and evaluation of an external control arm using prior clinical trials and real-world data. Clin Cancer Res 25:4993-5001, 2019
20. Li C, Ferro A, Mhatre SK, et al: Hybrid-control arm construction using historical trial data for an early-phase, randomized controlled trial in metastatic colorectal cancer. Commun Med 2:90, 2022
21. Schmidli H, Häring DA, Thomas M, et al: Beyond randomized clinical trials: Use of external controls. Clin Pharmacol Ther 107:806-816, 2020
22. Dron L, Golchi S, Hsu G, et al: Minimizing control group allocation in randomized trials using dynamic borrowing of external control data—An application to second line therapy for non-small cell lung cancer. Contemp Clin Trials Commun 16:100446, 2019
23. Loiseau N, Trichelair P, He M, et al: External control arm analysis: An evaluation of propensity score approaches, G-computation, and doubly debiased machine learning. BMC Med Res Methodol 22:335, 2022
24. Li F, Morgan KL, Zaslavsky AM: Balancing covariates via propensity score weighting. J Am Stat Assoc 113:390-400, 2018
25. Wu J, Li Y: Group sequential design for historical control trials using error spending functions. J Biopharm Stat 30:351-363, 2020
26. de Blank PM, Ostrom QT, Rouse C, et al: Years of life lived with disease and years of potential life lost in children who die of cancer in the United States, 2009. Cancer medicine 4:608-619, 2015

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