CLRM-17

USE OF EXTERNAL CONTROL DATA FOR PLANNING AND ANALYZING GBM TRIALS: READY FOR PRIME TIME?

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Randomized controlled trials (RCT) have been the gold standard for evaluating medical treatments for many decades. Randomization reduces systematic biases resulting from treatment or patient selection, whereby the improvement in clinical outcomes may be attributed to the experimental therapy under study. However, RCTs are often criticized for requiring large sample sizes and taking a long time to complete. For newly diagnosed glioblastoma (GBM), the clinical trial landscape has seen little progress since the establishment of the standard of care (SOC) by Stupp. Given the urgent need for better therapies, it has been argued that data collected from patients treated with the SOC from past GBM trials can provide high-quality external control data to supplement concurrent control arm in future trials, thereby increasing drug development efficiency by reducing the number of patients treated with SOC. Herein we consider a new design approach that leverages historical control data in the design and analysis of phase 3 GBM trials. At the first stage, patients are randomized with an equal probability to standard (concurrent control) arm and experimental arm. An interim analysis entails an outcome comparison between the concurrent and external control arms. If comparability is established, the external control data are carried forward to be combined with concurrent control data at the second stage where the randomization ratio is adapted to favor the experimental therapy, thereby reducing the number of patients treated in the concurrent control arm. Using completed phase 3 GBM trials, we elucidate the potential gain in design efficiency and draw caution to scenarios where it may fall short on meeting statistical criteria. We highlight practical challenges in its implementation and conclude that the new method is not ready for definitive phase 3 GBM studies at the current time. This work represents a critical appraisal of this new concept in GBM.

CLRM-18

SCREEN FAILURES IN PHASE III GLIOBLASTOMA CLINICAL TRIALS

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Glioblastoma (GBM) remains the most common and lethal malignant primary brain tumor in adult patients, with median overall survival ranging from 7 to 22 months. National Comprehensive Cancer Network guidelines encourage participation in clinical trials for both newly diagnosed and recurrent GBM patients. Multiple phase II trials in GBM have yielded promising, positive results, but the translation to phase III results is lacking and has failed to make strides in improving outcomes. These phase III trials universally require many participants, and the expenditure of phase III clinical trials is quite significant, with the median being 21.4 million dollars. With a paucity of ground-breaking phase III clinical trials and the cost expenditure to perform them, understanding screen failures in GBM clinical trials along with an evaluation of causes of screen failures is warranted. Using both ClinicalTrials.gov and PubMed, phase III clinical trials in GBM patients published from 1994 to 2021 were queried. This search, initially in ClinicalTrials.gov, involved using the terms: "glioblastoma" and "GBM" with filters "phase III," "interventional," "completed," "suspended," and "terminated." This search was cross-referenced with PubMed for published full articles in English peer-reviewed journals. Fifty-one studies were identified, and 21 out of 51 were appropriate for evaluation of screen failures, with 15 being for newly diagnosed GBM and six being for recurrent GBM. Nine out of 21 (42.9%) did not publish information on screen failures, and in the remaining 12 studies, proportions of screen failures ranged from 0-84.0% for newly diagnosed studies and 9.2-23.2% for recurrent studies, with a combined median percentage of 28.9%. In this analysis, over one-fourth of patients screen failed for GBM clinical trials. Thus, it is prudent to explore the causes of these screen failures, their implications on clinical trial design, and their impact on patient outcomes clinically, financially, and holistically.

CLRM-19

USING FUNCTIONAL PRECISION MEDICINE TO GUIDE CLINICAL TRIAL ENROLLMENT IN GBM

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Interventional clinical trials in glioblastoma (GBM) have been consistently disappointing, attributable to various factors such as ineffective therapies, inadequate trial designs including lack of control arms, or enrollment criteria that do not represent real-world practice. Novel paradigms for clinical trial design(s) in GBM are desperately needed to produce clinically useful patient outcomes. KIYATEC has developed a patient- and tumor-specific technology platform to evaluate cellular response(s) to therapeutics using 3D cell culture methods that provide functional, patient-specific response predictions. Employing KIYATEC's technology to screen compounds against both primary patient-, and PDX-derived specimens, enables clinical prioritization of early-stage assets most likely to have therapeutic response *in vivo*. In addition, KIYATEC's 3D Predict™ Glioma test has shown clinical correlation of test-predicted response(s) and clinical outcomes in GBM patients. Incorporating KIYATEC's 3D *ex vivo* technology into GBM therapeutic development is positioned to accelerate more successful trial results by 1) identifying early-stage compounds likely to possess clinical effects *in vivo*, and 2) prospectively identifying patients expected to have a clinical response to therapeutics in development. 3D Predict Glioma provides patient-specific responses within 7-10 days of tissue acquisition, providing an avenue for test integration into adaptive clinical trials, whereby functional characterization could provide gating information relating to trial execution. Specifically, functional response prediction may play a pivotal role in identifying newly diagnosed patients who might derive greater benefit from clinical trials compared to standard of care and by optimizing effective therapeutic selection in the recurrent setting. Therefore, a priori knowledge of an early-stage assets' potential, combined with therapeutic sensitivity of individual patient tissue, may facilitate a new era for adaptive clinical trial design by assimilating KIYATEC's analytically and clinically validated test into various steps of clinical trial execution such as randomization, stratification, therapy-switching, or compound addition/discontinuation.

CLRM-20

IDENTIFYING RISK FACTORS AND ANALYZING SURVIVAL FOLLOWING PACHYMENINGEAL FAILURE

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OBJECTIVE: Neurosurgery (NS) is an essential modality for large brain metastases (BM). As an adjuvant treatment, stereotactic radiosurgery (SRS) reduces neurocognitive toxicity without affecting post-treatment overall survival (OS) compared to whole brain radiation therapy. Pachymeningeal failure (PMF) beyond the SRS field is a relatively newly described entity, distinct from classical leptomeningeal failure (LMF), and unique to postoperative patients treated with adjuvant SRS. We sought to identify risk factors for PMF in patients treated with NS+SRS. METHODS: We reviewed a prospective registry (2009 to 2020) and identified all patients treated with NS+SRS. Clinical, radiological, pathological and treatment factors were analyzed. PMF incidence was evaluated using a competing risks model and differences between cohorts were measured using the Fine-Gray method. RESULTS: 144 Patients were identified. Median age was 62 (23-90). PMF occurred in 22.2% (32/144) patients). Univariate analysis indicated female gender (HR 2.65, p=0.013), higher GPA status (HR 2.4, p<0.001), absence of prior radiation therapy (HR N/A, p=0.018), controlled extracranial disease (CED) (HR 3.46, p=0.0038), and contact with the pia/dura (HR 3.30, p=0.0053) as risk factors for PMF. Piecemeal (vs En-bloc) resection also trended towards correlation (HR 2.07, p=0.054). Multivariate Analysis identified contact with pia/dura (HR 3.51, p=0.0053), piecemeal resection (HR 2.38, p=0.027), and CED (HR 3.97, p=0.0016) as significant correlates to PMF. PMF correlated with reduced OS (HR 2.90, p<0.001) but was improved compared to patients who developed LMF (HR 10.15, p= p<0.001). CONCLUSIONS: PMF is an underrecognized phenomenon that correlates with pre-operative pia/dura contact and piecemeal resection in patients treated with NS+SRS for BM. While less morbid than LMF, it is a critical event that deserves increased vigilance and analysis.

CLRM-21

RISK FACTORS ASSOCIATED WITH THE PRESENCE OF BRAIN METASTASIS AT THE MOMENT OF DIAGNOSIS IN LUNG CANCER PATIENTS: RETROSPECTIVE CASE SERIES

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BACKGROUND: Lung cancer (LC) is the second most frequent neoplasm worldwide and it is commonest origin of brain metastases (BM). The aim of this study is to identify clinical, histological and molecular variables associated with a higher risk of BM at diagnosis in LC patients. METHODS: A