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Negative trials over and over again: How can we do better?

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Over the past decade there has been significant progress in understanding the molecular pathogenesis of glioblastoma but this has not translated into better therapies for patients.[1] The negative phase III trials of rindopepimut, vocimagene amiretrorepvec, nivolumab, depatuxizumab mafodotin, and marizomib has now been joined by veliparib in newly-diagnosed glioblastoma with methylated MGMT promoter.[2] In contrast, there seems to be an explosion of new drug approvals in many other cancers. Why are we not doing better?

In other cancers, successful therapies are developed when they are directed against validated targets, show efficacy in predictive pre-clinical models, and achieve therapeutic concentrations and adequate inhibition of the putative targets in tumor tissue. In neuro-oncology these basic requirements are often not met before agents are taken to phase III trials. Too often we pursue targets without rigorous pre-clinical validation, we are often uncertain of an agents' ability to cross the blood–brain barrier (BBB) or whether it achieves adequate concentrations in the tumor, and often have insufficient evidence of target engagement and pathway modulation in situ. In addition, signal-finding studies are often flawed and poorly predictive of ultimate efficacy.

There are multiple reasons for these failures but six areas in particular need to be addressed: (1) the challenges posed by the biology of the tumor; (2) the lack of predictive pre-clinical models; (3) the lack of clinical trial infrastructure to efficiently evaluate novel agents, especially for early-phase trials; (4) suboptimal trial design and response assessment, (5) limited funding, and (6) the nihilistic psychology in our field.

Without doubt the biology of gliomas pose a particular challenge that other cancers often do not encounter, or at least not to the same degree. The BBB is a major challenge, preventing the majority of the universe of cancer drugs from reaching the tumor in therapeutic concentrations.[3] Evaluating the ability of agents to cross the BBB currently requires surgical "window-of-opportunity" studies to determine drug concentrations in enhancing and non-enhancing tumor tissue, and to determine pharmacodynamic effects. As useful as these surgical trials are, they are cumbersome and add several years of development time that is not encountered by extra-cranial tumors. Ideally, these trials would be replaced by non-invasive imaging of drug concentration and pharmacodynamic effects in the tumor using molecular imaging. There is a need for much more research in neuro-oncology evaluating these novel imaging approaches. The purposeful development of agents that cross the BBB effectively, and the use of novel techniques of BBB disruption, such as focused ultrasound and micro-bubbles, offer opportunities to increase the number of agents that can be used for brain tumor patients.

Other intrinsic aspects of glioma biology pose even more daunting barriers to progress. These include well known issues of tumor heterogeneity and redundancy of signaling pathways. Moreover, the recent recognition of the plastic nature of glioblastoma at the single-cell level suggests that transitions between single-cell glioblastoma states may confer resistance to targeted therapies, at least as monotherapy.[4] Still, the recent studies showing that agents targeting the MAP kinase pathway[5] and NTRK fusions[6] can have activity in selected groups of gliomas, including glioblastomas, offer hope. However, for the majority of tumors it is likely that combination therapies, and especially combination therapies exploiting synthetic lethality and addressing the plasticity of the different transcriptional states, will be necessary.

The risks of tumor biopsy pose a challenge in following an individual tumor's molecular evolution to guide appropriate therapy and clinical trial selection, often relying on outdated molecular markers from initial diagnosis. The difficulties of obtaining repeat biopsies makes using cell-free DNA (cf-DNA) in blood to evaluate tumor genotype particularly valuable in brain tumors but there are considerable challenges in developing these assays. Much more work focused on realizing the potential of these tests is required. In the interim, greater evaluation of cf-DNA in cerebrospinal fluid and strategies to

disrupt the BBB and increase the yield of cf-DNA in blood and CSF with focused ultrasound should be explored.

The lack of predictive pre-clinical models is a second major barrier to progress. The old tumor cell lines that do not replicate tumor genotype have been replaced by primary neurosphere lines and patient-derived xenografts (PDX). These have greater fidelity to the genotype in patient tumors and model response to temozolomide but grow slowly and unfortunately may not be much more predictive. The recent Alliance AO71102 trial of veliparib was based on pre-clinical studies showing benefit in MGMT promoter-methylated glioblastoma PDX models.[2,7] To date, we still lack evidence that these models predict outcome in patients. These limitations are even more pronounced in models evaluating immunotherapies. While it is likely that pre-clinical models can be used to screen out agents that do not show activity, only agents that showed large therapeutic benefits should be taken into the clinic. Studies showing modest but statistically significant improvements are unlikely to lead to real benefit in patients. There is a critical need for better models that more rapidly and reliably predict benefit in patients, and for a system to effectively share these models so that they are widely available. Given how poor pre-clinical models predict outcome in trials, there should be greater emphasis in evaluating novel therapies early in development in patients using surgical "window-of-opportunity" studies to determine whether the desired pharmacodynamic effects are achieved and to obtain preliminary signals of efficacy.

A third barrier to progress is the ineffective and inefficient clinical trial infrastructure used to develop novel therapies for gliomas. The lack of early-phase clinical trial networks to conduct phase I studies and surgical "window-of opportunity" trials to screen drugs for further development is a major impediment to progress. While the Adult Brain Tumor Consortium had important limitations there is a need to develop an adequate replacement. The new National Cancer Institute (NCI) sponsored Glioblastoma Treatment Network is trying to fulfill this need but requires increased funding for a viable clinical trial component in order to be an adequate replacement.

A fourth issue relates to wide variability in patient outcomes, limiting the reliability of uncontrolled single arm studies in predicting benefit, especially for newly-diagnosed glioblastoma patients. The new 2021 World Health Organization Central Nervous Tumor Classification will hopefully allow patients with more homogenous prognosis to be enrolled into clinical trials, reducing this variability in outcomes. The ongoing Response Assessment in Neuro-Oncology efforts, including the planned RANO 2.0, will also increase reliability in response assessment. Currently, novel therapies being evaluated in newly-diagnosed glioblastoma patients require randomized controlled trials. To increase the efficiency and reduce the patient numbers and resources required, a number of platform trials using Bayesian adaptive randomization are in progress, including the Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT)[8] and GBM AGILE (Adaptive Global Innovative Learning Environment)[9] trials. More studies exploring the value of external control arm data to replace historic controls should also be performed to see if this approach can replace the need for concurrent control arms in screening trials, as well as potentially reducing the number of patients in the control arm in randomized studies.[10]

The fifth challenge is the limited funding available to do many of the required pre-clinical and clinical studies discussed above. There is a need for stronger commitment from the NCI and for the field to evaluate more novel funding options including greater collaboration with venture capital.

The final major hurdle is the psychology in neuro-oncology where repeated failures have lowered the bar for what trials are considered acceptable. Many of the failed phase III trials were launched with inadequate pre-clinical and signal-finding clinical data. We owe it to our patients to be much more rigorous in determining whether specific agents should be developed. Trials that we would not put our loved ones on probably should not be conducted.

The recent advances in our understanding of glioblastoma biology provide us with the opportunity to develop better therapies for our patients. However, there is much more work to be done.

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