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Baseline Requirements for Novel Agents Being Considered for Phase II/III Brain Cancer Efficacy Trials:

Conclusions from the Adult Brain Tumor Consortium's First Workshop on CNS Drug Delivery

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In the past thirty years, only one drug (temozolomide) has been found to modestly improve survival in patients with glioblastoma.[1] This lack of progress is remarkable given the thousands of patients accrued to brain cancer trials, recent discoveries of relevant molecular pathways, availability of next generation sequencing panels to identify underlying tumor mutations, proliferation of targeted therapies, and progress seen in other "resistant" cancers. A major factor distinguishing brain cancers from other malignancies is the presence of the blood-brain barrier. This evolutionarily conserved barrier severely restricts the entry of over 95% of FDA approved drugs into the central nervous system (CNS).[2,3] As a result, the failure to improve survival in patients with glioblastoma is likely related to our inability to deliver therapeutic drug concentrations to tumor cells 'protected' by the blood-brain barrier.[4,5] Historically, clinical investigators have used pharmacokinetic data (such as "measurable" concentrations in animal or human brain tumor specimens or blood to brain concentration ratios) to justify proceeding with glioblastoma efficacy trials. Unfortunately, this approach has not been productive.[6]

This workshop was designed to reassess what information on the penetration of systemically administered anti-cancer drugs into brain tumors should be available when a novel agent is being considered for phase II/III efficacy trials in patients with glioblastoma. The workshop focused solely on agents that require direct contact with glioblastoma cells to be effective, such as pathway or mutation-targeted agents or chemotherapy drugs with efficacy in other cancers. It did not consider novel agents with mechanisms of action that may allow for efficacy without blood-brain barrier penetration such as vascular endothelial growth factor (VEGF) targeted agents, vaccines, checkpoint inhibitors, or other immunotherapy approaches. This workshop resulted in three major conclusions designed to ensure that agents selected for future phase II/III efficacy trials have the best chance to improve survival in patients with glioblastoma.

Conclusion #1: Drug Must Reach the Tumor in Therapeutic Concentrations

Given the almost universal failure of clinical trials in patients with glioblastoma and the fact that the blood-brain barrier provides a formidable barrier to drug entry into the brain, it is crucial to know if the drug actually reached the tumor in therapeutic concentrations. In order to answer this question, two pieces of information are required. First, one must determine the concentration of the administered drug within the tumor tissue. Measuring intratumoral drug levels is usually accomplished by giving the medication of interest prior to a planned surgical resection and analyzing total drug concentrations within the resected tissue, typically in contrast-enhancing tumor. Alternatively, microdialysis catheters can be placed in residual tumor tissue at the time of surgery and post-operatively the drug of interest can be administered systemically with serial acquisition of samples from the microdialysis catheters. This will provide concentrations of free drug within the extracellular fluid of the brain tumor.[7-9] Alternatively, in vitro-in vivo extrapolation has been utilized as an alternative method for estimating unbound drug concentrations in the brain.[10,11] This relies on physiologically based pharmacokinetic modeling that requires a deep understanding of the conditions of in vitro experiments and the pathophysiology of tumor-bearing brain to predict the systemic and CNS pharmacokinetics of a drug. Although attractive, results can be misleading when non-physiologic conditions are present.

Second, it is critical to understand what concentrations of the administered drug are required to demonstrate antitumor activity or to modulate a relevant target. This information is surprisingly difficult to find for many established and novel drugs and may need to be prospectively studied using in vitro methods, animal models, or data from patients with systemic cancers where blood concentrations are assumed to be more similar to tumor concentrations than they are in brain tumors. Obviously, if major discrepancies exist between the drug concentration required for antitumor activity and the actual concentrations measured within the tumor, it would be unlikely that a phase II/III efficacy trial would be positive. Using an infectious disease analogy, if the

concentrations of an antibiotic in infected tissue are far below the minimal bactericidal concentration, the proposed treatment is unlikely to provide the desired clinical benefit.

Conclusion #2: Therapeutic Concentrations of Drug Should be Present within the Entire Tumor Volume

For decades the medical literature has documented the extensive infiltration of glioblastomas within the CNS even when these tumors appear relatively localized on radiographic studies. Even extensive surgical procedures, including hemispherectomies, do not result in cures as residual tumor always remains post-operatively.[12] As a result, after surgery all patients are referred for radiation and possible chemotherapy. While radiation oncologists routinely target both the contrast enhancing and non-enhancing tumor seen on MRI scans, neurosurgeons and neuro-oncologists often focus on the contrast enhancing tumor volume. In neurosurgery a "gross total resection" of a glioblastoma is commonly defined by the removal of all contrast enhancing tumor even when extensive T2 signal on the MRI, which is known to contain active tumor, remains post-operatively.[12] Similarly, neuro-oncologists typically measure complete and partial responses based on changes in the contrast-enhancing portion of glioblastoma regardless of the residual T2 signal abnormalities. This is similar to focusing on the visible tip of an iceberg rather than the much larger, but submerged, ice mass. The critical importance of the non-enhancing residual cancer is easily appreciated when looking at the modest survival benefits following gross total resections with removal of all contrast enhancing tumor.[13-17] By extrapolation, a systemically administered chemotherapeutic agent that only reaches therapeutic concentrations within the contrast enhancing tumor (where the blood-brain barrier is known to be disrupted) is unlikely to be more effective than a gross total resection at the hands of an experienced neurosurgeon. As a result, significant improvements in the survival of patients with glioblastomas are likely to occur only if tumor in non-enhancing brain also receives therapeutic concentrations of an effective pharmaceutical agent. The non-enhancing tumor bearing region is

complex as it also contains edema and at the time of recurrence radiation related tissue injury. [18,19] This region is understudied and deserves to be a high priority for future research.

Conclusion #3: It is the responsibility of pre-clinical and phase I investigators to: 1) determine a "therapeutic" target concentration of a novel agent and 2) provide evidence that this concentration can be reached in non-enhancing brain tumor tissue before a novel agent should be considered for efficacy trials in patients with glioblastoma.

Moving forward, a clear insight into these two questions is critically important for prioritizing therapies to move into Phase II/III clinical trials. While there is no "one-size fits all" strategy to answer these questions, some common strategies could be employed. First, further research must be performed to better characterize the relevance and limitations of pre-clinical glioblastoma tumor models as they relate to blood-brain barrier integrity and the microenvironment within orthotopic tumors. This analysis could provide a more clear understanding of how to use these models to predict intra- and inter-patient pharmacokinetic and pharmacodynamic behavior in human glioblastomas. Second, clinical studies evaluating drug distribution via surgical sampling, microdialysis or direct drug imaging could be performed earlier during the drug development process, and these studies should be designed to explicitly define intra-tumor heterogeneity in drug delivery across a population of patients. Third, although significant strides have been made, education and awareness efforts need to be increased to ensure that clinical scientists, drug

developers and regulators all have a clear understanding of the critical importance of these issues. Without robust buy-in from all key stakeholders, progress will continue to be slow. Thus, these priorities should be incorporated into the peer review process involved in protocol development, protocol approval, and presentations in scientific meetings and publications. Coupled with a requirement to better understand nuances surrounding drug distribution into brain tumors, foundation, industry and government agencies should prioritize funding both pre-clinical and clinical experiments to specifically address these issues prior to the initiation of definitive Phase II/III clinical testing.

Summary

The primary message from this ABTC workshop is that significant improvements in the survival of patients with glioblastoma will likely require that tumoricidal or biologically active concentrations of therapeutic agents be achieved in non-contrast enhancing tumor bearing regions of the brain (Table 1). Each portion of this statement presents novel challenges and tasks for pre-clinical and phase I investigators that have been largely overlooked in the development of brain tumor trials. The use of these more rigorous drug delivery evaluations will encourage pre-clinical and phase I investigators to determine a therapeutic concentration for each agent under study and to carefully define the CNS penetration of new drugs. The results of these studies, when coupled with the standard documentation of substantial survival improvements in animal models and/or sustained clinical benefit in patients, should improve: 1) the selection of therapeutic agents being tested in future efficacy trials and 2) the likelihood of genuinely prolonging survival in patients with these difficult to treat malignancies.

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Table 1: Preclinical and Phase I outcomes that would provide crucial information before agents are considered for efficacy trials in patients with glioblastoma

1. Estimating a minimal acceptable "therapeutic" concentration for drug of interest
A) Effective concentrations in vitro B) Effective concentrations in vivo in systemic cancers where blood-brain barrier is not an issue a. Animal models b. Other human cancers C) Concentrations that significantly change critical pharmacodynamic markers in vitro or in vivo
2. Estimating the ability of the drug to cross the blood-brain barrier
A. Standard considerations: molecular weight, lipid solubility, charge, protein binding, etc. B. Penetration using in vitro blood-brain barrier models C. Drug concentrations in animal models after systemic administration I. Surgical biopsies or autopsy studies II. Microdialysis III. Imaging
3. Pharmacokinetics: Drug concentrations in non-enhancing human brain tumor tissue following systemic administration
A. Target directed biopsies or intra-operative studies B. Microdialysis C. Imaging the distribution of the administered drug
4. Pharmacodynamics: Drug effect on non-enhancing human brain tumor tissue following systemic administration
A. Tissue endpoints (pathway inhibition, apoptotic index, proliferative index, metabolic changes, etc) B. Other endpoints (flow cytometry, hypoxia, etc.)