

How can we develop therapies for glioblastoma more efficiently? Randomized versus single-arm studies

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Despite extensive efforts, progress in finding more effective therapies for patients with glioblastomas has been disappointing. With the modest exceptions of temozolomide, bevacizumab, and tumor-treating fields (TTF) there have been few advances over the past two decades, and median survival for glioblastomas remains only 14–18 months.¹

The development of novel agents for glioblastomas has followed the standard paradigm in oncology where a new therapy is first evaluated in recurrent disease, and if it shows activity it is then advanced for evaluation in the first-line setting. This approach ensures that agents demonstrate single-agent activity before being used in the adjuvant setting, either alone or in combination with standard therapies. While reasonable, this approach has unfortunately not led to the identification of any effective therapies for glioblastomas. In fact, studies of temozolomide and TTF showed minimal responses in recurrent glioblastomas, and randomized studies comparing these treatments against standard therapies failed to demonstrate significant benefit. In contrast, trials evaluating temozolomide and TTF in the first-line setting showed modest, but significant survival benefit, leading to regulatory approval of both therapies.^{1,2} These results raise the important question regarding the optimal time to evaluate novel therapies for glioblastomas.

As with other advanced cancers, there is increasing data suggesting that as glioblastomas evolve and develop resistance to initial therapies they are more molecularly complex and heterogeneous,³ while at the same time the immune system is more suppressed, making recurrent tumors harder to treat. For targeted agents, tumor genotype at diagnosis may have only limited relevance to the optimal targets in recurrent tumors, and the increasing molecular heterogeneity decreases the likelihood of single agents or even combinations of agents being effective.

This scenario of molecularly advanced cancer being more difficult to treat than early-stage disease is found in many other

cancers, such as the use of imatinib mesylate (Gleevec) for chronic myelogenous leukemia (CML). Use of imatinib mesylate as therapy in chronic-phase CML results in a 49–88% complete cytologic response rate and a 5-year progression-free survival (PFS) of 83%–94%,⁴ whereas use of the same agent for accelerated CML produces a complete cytologic response rate in only 21% of patients with a much reduced 5-year PFS. Similarly, the effectiveness of immunotherapies for recurrent disease may be limited by the suppressed immune system after standard radiation therapy and temozolomide chemotherapy,⁵ reducing their chances for success. Given these challenges in treating recurrent glioblastomas perhaps there should be a greater emphasis on evaluating novel therapies in the first-line setting where moderately effective agents may have a better chance of improving patient outcomes. Hopefully, there will eventually be truly effective agents that will be beneficial to patients regardless of their stage of disease.

Evaluating novel agents in newly diagnosed glioblastoma patients poses a number of important challenges. Without clinical evidence of single-agent activity in recurrent disease the preclinical data supporting the use of the agent in glioblastoma in first line must be robust, and ideally these agents must show good penetration across the blood-brain barrier when relevant, and synergy with radiation therapy and /or temozolomide. Clinical trials in newly-diagnosed glioblastomas are more complex than trials in recurrent disease, requiring a significantly longer time to determine efficacy and a larger number of patients. Phase I studies of novel agents with radiation therapy and temozolomide in first line are particularly time consuming, often taking 1–2 years given the typical 8- to 10-week dose-limiting toxicity evaluation period required for each cohort. The challenges in glioblastoma are compounded by the limited number of patients available for enrollment into clinical trials compared to many other cancers and by the fact that earlier

non-survival endpoints such as PFS are relatively unreliable due to issues related to pseudoprogression.⁶ Given these challenges there is a need to improve the design and conduct of trials in newly diagnosed glioblastoma.

In this issue of *Neuro-Oncology*, Grossman et al. discuss one of the major challenges in the design of phase II trials for newly diagnosed glioblastomas: the use of single-arm studies versus randomized studies.⁷ The goal of these studies is to select promising therapies for definitive phase III testing and to eliminate ineffective treatments. The attraction of single-arm phase II trials is the requirement of fewer patients and resources and the avoidance of enrolling patients into unattractive control arms with standard therapies that are barely effective. However, single-arm phase II studies are only valid if there are reliable historic data for comparison. This is becoming an increasingly important limitation as historic data for patients with specific molecular subsets for studies with targeted molecular agents, or specific eligibility criteria such as gross total resection and restricted corticosteroid use for immunotherapy studies, are generally not available. The failure of an increasing number of single-arm phase II trials to accurately predict outcome in phase III trials (cediranib,⁸ enzastaurin,⁹ cilengitide,¹⁰ and rindopepimut¹¹) suggests that this approach is unreliable and should be used sparingly, if at all. Randomized phase II studies require significantly more resources and include control arms with standard therapies but are likely to be more predictive of benefit in subsequent phase III trials, and they are ultimately a better use of resources. Nonetheless, standard randomized phase II trials are relatively inefficient, slow, and utilize significant resources, especially if separate control arms are used for each study.

To improve on the current design of randomized phase II studies, a number of efforts are underway to conduct novel multi-arm biomarker-driven studies using Bayesian designs and adaptive randomization similar to the I-Spy studies in breast cancer. These trials achieve efficiencies by sharing a control arm and by potentially requiring fewer patients and eliminating ineffective agents more rapidly. Examples of such trials include the randomized phase II study Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGHt) for newly diagnosed glioblastoma with unmethylated MGMT promoter (NCT02977780) and GBM AGILE (Adaptive Global Innovative Learning Environment), an international trial evaluating both newly diagnosed and recurrent glioblastomas with registration capabilities. Other innovative efforts to accelerate the screening of novel therapies for newly diagnosed glioblastoma include the National Center For Tumor Disease (NCT) Neuro Master Match (N2M2) trial in which patients with newly diagnosed glioblastoma with

unmethylated MGMT promoter are genotyped using the 450K array and assigned to specific buckets with targeted molecular agents or immunotherapies. Hopefully, these novel randomized designs will accelerate the screening of novel agents for glioblastoma and improve our ability to identify effective agents for our patients.

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