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Editorial
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Current Challenges in the Treatment of Glioblastoma

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Editorial

Glioblastoma Multiforme (GBM) refers to the most malignant and prevalent type of glioma and thus is aptly named. GBMs are molecularly heterogeneous despite histologic similarities with other GBMs [1]. It is precisely this "multi-form" heterogeneity which hinders therapeutic advancement. Despite decades of research, overall survival (OS) remains abysmal at ~15 months from date of surgical diagnosis [2].

Identifying the Challenges

The standard of care for GBMs is maximal safe resection followed by 6 weeks of radiation therapy (XRT) with concurrent daily temozolomide (TMZ), followed by at least 6 months of adjuvant TMZ [3]. This Stupp regimen was established in 2005, but unfortunately remains the standard of care over ten years later. Although it is designated for all newly-diagnosed GBM patients up to the age of 70, it was observed that certain GBMs had inherently different disease courses and treatment responses to the same regimen. In 2005 the activity of the DNA repair gene MGMT (O^6-methylguanine-DNA methyltransferase) was noted to predict responses to TMZ treatment and survival outcomes [4]. Significant advances involving the discovery of important molecular pathways of GBMs have been made since the advent of the Stupp regimen, yet no systemic treatment to date has been proven to be superior to the Stupp regimen. In 2015, the addition of Novo-TTF (tumor-treating fields) to the Stupp regimen resulted in increased OS and progression-free survival (PFS) compared to patients who received Stupp regimen without Novo-TTF [5]. Subsequent trials involving Novo-TTF are necessary to validate the results of this study.

Limited Access to Clinical Trials

Approximately 12,000 new GBMs will be diagnosed in 2016 [6]. Unfortunately, only about 10-20% of malignant glioma patients will enroll in a Neuro-Oncology clinical trial [7]. There are multiple factors accounting for this, including lack of access to neuro-oncologists or brain tumor centers, insufficient resected tumor tissue to qualify for targeted therapeutic trials, as well as physician and patient preferences. Neurosurgeons who routinely perform maximal safe resections, as opposed to stereotactic biopsies only, are critical to increasing trial accrual. Such procedures are important to obtain as much tumor tissue as safely possible for molecular analyses. In addition, the advice of the treating physician greatly influences patients' attitudes toward clinical trial participation. Community medical centers without brain tumor centers are unlikely to have clinical trials for brain tumors. Furthermore, physicians who see only a small number of glioma patients may have a nihilistic attitude towards these patients, and thus may not encourage patients to seek brain tumor trials. It is critical to convey to the medical community that clinical trials are the most direct method of identifying promising therapies for GBM patients.

Despite these challenges, a number of high-accruing clinical trials have been completed over the years. The Stupp trial included a total of 573 patients from 85 centers in 15 countries through several cooperative clinical trial groups. These patients were enrolled in approximately 2 years, which is a remarkably short accrual period [3]. Another example involved a trial for newly-diagnosed GBM patients in which patients were randomized to receive Stupp regimen plus IV Bevacizumab versus Stupp regimen plus IV placebo [8]. In approximately 2 years, 978 patients were enrolled, and of those patients 637 patients were randomized; again, multiple brain tumor consortia participated. These examples illustrate that a large number of patients with an uncommon cancer can be enrolled efficiently through coordinated efforts by investigators, treating physicians, and patients.

Tumor Heterogeneity

One of the biggest challenges in finding effective treatments involves the multiple molecular

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pathways of GBMs. Identifying just one target is insufficient, as this method does not account for the considerable array of molecular variabilities found within and among GBM patients [9]. A targeted treatment may be effective in neutralizing a particular molecular target. However the target may not have clinical effect because it may be a bystander target rather than a true molecular driver of GBM growth and migration. This is illustrated from the negative results of GBM trials involving single-agent EGFR (Epidermal Growth Factor Receptor) inhibitors [10].

Effective treatment regimens will likely require combination therapies that target multiple molecular aberrations. Novel trial designs are being formulated that take into account the above challenges and attempt to overcome them. One interesting trial design for GBM begins with multiple biopsies of the tumor tissue from both the enhancing disease and the more infiltrative, non-enhancing disease. The tissues would be analyzed for genomic profiling and up to 4 drugs would be selected for an individual by a multi-specialty tumor board [9].

Inadequate Clinical Applications

There is undoubtedly a spectrum of survival outcomes within the GBM patient population due to the molecular tumor heterogeneity [11]. Identifying these molecular signatures does not always lead to new treatments; in fact, the recently discovered molecular knowledge has far outpaced its clinical applications. Approximately 30% of tumors have methylation of the MGMT promoter gene, which inactivates its repair activity, and thus allows TMZ to be more effective [12]. However, patients with GBMs that are MGMT unmethylated are still given the Stupp regimen, as there is no proven effective alternative treatment regimen for the unmethylated patients.

More recent clinical trials for newly-diagnosed GBMs have begun to stratify trial patients by MGMT promoter methylation status. This trial design allows for MGMT unmethylated patients the opportunity to receive a potentially effective experimental agent concurrently with XRT without TMZ, thus minimizing the potential side effects to determine an effective alternative regimen for these patients.

Drug Delivery and Distribution

Adequate drug delivery and distribution is another tremendous challenge in identifying effective GBM therapies due to the presence of the blood-brain barrier (BBB). Some agents are completely excluded from entering the brain, while others are unable to reach the tumor in sufficient concentrations to have adequate anti-tumor effect. Enhancing disease noted on contrast MRIs is ideally resected at initial diagnosis, leaving the residual infiltrative non-enhancing disease with a more intact BBB [9]. In addition, the residual non-enhancing tumor may have different molecular aberrations compared with the enhancing resected tumor that is actually analyzed. Thus, a critical part of solving the BBB challenge is the timing of drug delivery within the context of surgical intervention. Molecular profiling has provided significant clinical applications in other cancers, but repurposing these treatments for GBMs has thus far proven unsuccessful due to lack of BBB penetration or inadequate distribution. The primary reasons TMZ has remained the primary neuro-oncology chemotherapy agent is its excellent BBB penetration, favorable toxicity profile, and oral formulation. The advantages of TMZ over many other drugs should be taken into consideration when designing new treatments.

Conclusion

Advances in the treatment of GBM have been unacceptably slow for a multitude of reasons, including limited access to brain tumor clinical trials, tumor heterogeneity, and poor drug delivery/distribution failure due to the BBB. These factors result in significant difficulty translating scientific advances in Neuro-Oncology into effective clinical applications. Knowledge of the molecular landscape of glioblastomas has increased exponentially over the last several years, but the laboratory science is still significantly ahead of clinical applications. Tissue-based clinical trials that focus on the molecular profile of the individual tumor are likely to yield more informative and applicable results than traditional non-selective trials. If given the proper information and motivation, patients can and will participate in Neuro-Oncology trials. Although these challenges are quite daunting at this time, the field of Neuro-Oncology will eventually conquer them to develop truly effective therapies for this devastating disease.

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