Understanding and Treating Glioblastoma

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KEYWORDS

• Glioblastoma • MGMT • Repositioning of drugs • Precision medicine • Biomarker • Radiomics • Treatment resistance • Immunotherapy

KEY POINTS

- Molecular biomarkers are entering diagnostics in neurooncology; current efforts aim at developing biomarkers-based treatment concepts.
- Understanding and overcoming resistance at multiple levels is the key challenge in glioblastoma; reviewing the failure of past concept-driven approaches such as antiangiogenic therapies or trials of unselected populations is necessary.
- The failure of recent immunotherapy trials should provide lessons for future development.
- Despite limited options to molecularly stratify glioblastoma into different age groups, patient functional status and age are key factors to consider for treatment decisions.

INTRODUCTION

The natural disease course in glioblastoma (GB) is invariably grim. A clinical event (eg, a seizure) or a cerebral image incidentally triggers clinical workup, commonly resulting in a maximal safe surgery. Diagnosis is made by careful neuropathological assessment of the tissue, including immunohistochemistry and selected molecular tests. Adjuvant treatments include radiotherapy (RT) to an area of the brain defined by the contrast-enhancing volume plus a safety margin, as well as alkylating chemotherapy with temozolomide (TMZ).[1] Variation at this stage is limited and may include modification of RT (and sometimes chemotherapy) according to age,[2] and the intensification or omission of alkylating chemotherapy according to the methylation status of the promotor region of the *O^6-methylguanine DNA-methyltransferase* (MGMT) gene[1,3,4] and

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Neurol Clin 36 (2018) 485–499
https://doi.org/10.1016/j.ncl.2018.04.006
neurologic.theclinics.com

potentially point mutations in the promoter of the *telomerase reverse transcriptase* (*TERT*) gene, resulting in increased telomerase expression.[5]

Currently available GB treatments are not curative but there are subgroups of patients who derive greater benefit from current treatments, radiation, and alkylating chemotherapy, as well as experimental targeted or immune therapies. Features hampering treatment efficacy across many cancers are prominently present in GB: rapid and infiltrative growth, most likely imitating features of normal brain development[6]; clonal heterogeneity with a component of primitive (or stem-like) features, varying over time with treatment selection[7]; and pathologic angiogenesis, resulting in a hypoxic and immunosuppressive microenvironment.[8]

Whereas the concept of molecular subclassification defined by gene expression and DNA methylation has been spearheaded[9] and further refined[10,11] in GB, the immediate clinical impact on the diagnostic classification,[12] treatment, or even trial development has remained limited. Consequently, trials to date do not use epigenetic or genetic criteria to biologically subdivide GB. *MGMT* promoter hypermethylation (despite its relevance as a predictive marker for response to alkylating chemotherapy) has almost no impact on clinical decision-making, except perhaps in elderly patients.

Understanding of molecular characteristics and cell intrinsic mechanisms of GB pathogenesis has evolved in the last decade.[6,9–11,13] The updated 2016 World Health Organization classification of central nervous system tumors[12] integrates genotypic and phenotypic parameters to GB diagnostics, notably the presence or absence of *isocitrate dehydrogenase* (*IDH*) mutations. These and other mutated drivers in GB are putative targets for treatment. Recent studies in colon cancer revealed that subjects with mismatch repair deficiency (dMMR) respond better to anti-programmed death (PD)-1 therapy.[14] Additional studies indicate that other solid tumors with MMR deficiency, including GB, are sensitive to anti-PD1 therapy.[15,16] There is increasing effort to integrate molecularly informed diagnoses into therapy decision-making.[17–19] Although precision medicine in cancer proposes that genomic characterization of tumors can inform personalized targeted therapies, this proposition is complicated in GB by spatial and temporal heterogeneity.[20]

In parallel with the generation of increasingly complex molecular models for ex vivo data analysis, advanced MRI and data analysis (eg, radiomics) are being developed to decipher information about tumors noninvasively.[21]

Despite all efforts and successes in other solid tumors and the enormous power of basic science in neurooncology, a lack of stringent integration of the existing knowledge into clinical (research) practices has left GB lagging behind the current evolution of modern oncology. The focus to date on traditional all-comers trials, as well as the dearth of widely accepted molecular tests and subsequent enrichment strategies, are important obstacles. An example of concepts in which selection might have made a difference includes the antiangiogenic studies with bevacizumab. Despite the post hoc development of a predictive RNA expression signature favoring bevacizumab treatment in proneural subtypes,[22] the proof-of-concept study has still not been planned. Other examples of putative biomarkers that can be used for subject selection include methylation levels for CpG2 in the region of the *CD95 ligand* (*CD95L*) gene promotor as a predictive biomarker for the CD95L inhibitory recombinant protein asunercept combined with reirradiation in recurrent GB[23] and mechanistic target of rapamycin (mTOR) Ser2448 phosphorylation as a predictive biomarker for the mTOR inhibitor temsirolimus in newly diagnosed GB.[24]

In GB, which harms patients by locally destructive brain growth as opposed to systemic metastases, immunosuppression has been extensively studied. Multiple pathways are proposed to mediate GB-associated immunosuppression.