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Current Trends in High-Grade Gliomas

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Abstract

This is an overview of the current trends in the management of high-grade gliomas based on the current evidence available at the time of compiling this chapter in the first quarter of 2016, by a dedicated, high-volume Neurosurgical Oncology team of clinical and surgical Neuro-Oncologists based in central Pennsylvania.

Keywords: High-grade glioma, glioblastoma, malignant brain tumor, brain tumor, intrinsic glioma

1. Introduction

The year 2016 continues to be both an enlightening and an exciting year for advances in the investigation and management of high-grade gliomas. The hallmark of glioblastomas is their molecular and genetic heterogeneity, the ability to infiltrate diffusely and undergo rapid neoangiogenesis, while actively challenging our current combinatorial therapeutic approach. At the time of writing, over 230 clinical trials were open in the USA, with ongoing recruitment or due to start. This overview of current trends will involve the details of the molecular markers now in use for both the diagnosis and prognostication of high-grade gliomas, updates on neuroimaging guidelines for both de novo and secondary high-grade gliomas, and the discussion of potential adjuvant therapies to the current standard of care.

2. Twenty-first century epidemiological trends

The most recent 2015 Statistical Report of the Central Brain Tumor Registry [1] documents the epidemiology of glioblastomas from 2008 to 2012. Glioblastomas remain the most common malignant histology (46.1%) of all primary malignant brain tumors, with an age-proportional incidence peaking at the ninth decade of life (age range 75-84 years). Of interest, glioblastomas have been shown to be 1.6 times more common in males, twice as common in Caucasians, and only 5.1% of patients survive five years after diagnosis.

3. The genetic risk of glioma

The lifetime risk of gliomas is 4-5 per 1000 of the general population. Thus, inheriting of one of the low penetrance glioma risk variants may increase the risk by 20-40% to approximately 6 per 1000 [2]. The risk loci of glioma variants have been identified as ten inherited variants near eight genes, 2 with stratification leading to an increase in the risk of developing gliomas.

The common inherited variants are named for the nearby genes of TERC, TERT, EGFR, CDKN2B, PHLDB1, CCDC26, TP53 and RTEL1, and are not directly involved in protein coding [3]. Of interest, these variants increase the odds ratio of gliomagenesis on a scale of 1.2-1.4. TERT, TERC, and RTEL1 are involved in telomere maintenance, and it has been hypothesized that a longer telomere length may possibly contribute to risk of gliomas [4, 5]. Additionally, of note, is the predictive and prognostic value of gliomas with TERT gene promoter mutations in association with isocitrate dehydrogenase (IDH) mutations and loss of heterozygosity of 1p/19q [4]. The less common risk loci are noted to correlate with higher odds ratios, and these are located near TP53 (2.4-fold increase in relative risk) and CCDC26 (6.3-fold increase in relative risk) especially in the presence of an IDH mutation or an oligodendroglial component. Moreover, the UCSF Adult Glioma Study noted that population screening for the risk loci near the CCDC26 yielded significantly more false positives than true positives, and hence the yield for undertaking this screening test of risk loci was extremely low [2].

At this point, with our current knowledge arsenal, the authors advise the following three acquired molecular glioblastoma markers to be identified and then further correlate to survival and outcome: IDH mutation, 1p/19q, and TERT promoter mutation. These molecular glioblastoma markers are then further subdivided into five glioma subgroups to further elicit the pathways of gliomas in pathways: TERT mutated only (most common in approximately half of the cases), IDH mutated only, TERT and IDH mutation (least common), triple negative and triple positive [6, 7]. Of note, the IDH mutation status was analyzed in the BELOB trial, which showed a lower median overall survival for patients with wild-type IDH (8 months) compared with median survival of 20 months for patients with an IDH mutational status [8]. We also note here, in our clinical role as Neurosurgical Oncologists, of the recent landmark paper associating a definite survival benefit after maximal surgical resection, including both enhancing and nonenhancing tumor, resulting in an improved prognosis observed in the IDH1 mutant subgroup [9]. Thus, individualized surgical strategies for high-grade gliomas must be considered on the molecular IDH marker status of the tumor [10].

The recent development of a targeted next-generation sequencing panel (GliSeq) provides simultaneous, highly accurate and comprehensive genetic profiling of a wide array of central nervous system (CNS) tumors on an increasingly smaller volumes of biopsies in a single workflow format [11]. This next-generation assay allows simultaneous detection of the major mutations (>1360 hot spots in 30 CNS tumor-related genes) in addition to 14 gene fusions and 24 gene copy number changes in a rapid and cost-effective manner. We look forward to the incorporation of the versatile GliSeq as a high throughput technological advance to rapidly identify a variety of genetic alterations and small deletions, thereby assisting in diagnosis and prognostic stratification of brain tumors.

Finally, the Neuro-Oncology community looks forward to the Glioma International Case-Control Consortium undertaking the important task of identification of new risk loci by the genotyping of 4000 glioma and 4000 nonglioma patients in the Epi4K project (epgb.org/epi4k).

4. Neuro-radiological updates for high-grade gliomas

The updated aims of the working group of the Response Assessment in Neuro-Oncology (RANO) continue to provide guidelines for a uniform criteria for the assessment of determining the progression and treatment response of high-grade gliomas [12]. RANO guidelines will be discussed in detail here, as it is imperative to emphasize the clinical need for consistency and standardization of imaging, for a reliable assessment of tumor burden and progression.

The RANO guidelines refer to the reliability of imaging data and reproducibility of the acquired results to be undertaken no later than 72 hours postsurgical resection and is determined by the standardization of gadolinium dose, slice thickness ≥ 5 mm or no more than twice the thickness of a measurable lesion. We now describe RANO guidelines nomenclature as per the updated guidelines [12, 13]:

- **Measurable lesions** are bidimensionally contrast-enhancing, with clearly defined margins in two perpendicular diameters, each measuring at least 10 mm in diameter.
- **Nonmeasurable lesions** refer to those with maximal diameters of <10 mm, masses with poorly defined margins (cysts, necrotic lesions, and leptomeningeal tumors) and nonenhancing lesions only seen on FLAIR/T2. Hence, for nonmeasurable lesions, continued radiological surveillance may indicate only the attainment of clinical plateau of stable disease, versus the response rate of measurable lesions as a response or failure to therapy in radiological follow-up.

Furthermore, there are four RANO categories to treatment response:

- Complete response

This refers to the lack of all enhancing lesions for a minimum of four weeks and the appearance of new lesions, this should be married to the patients' clinical picture of stability or response, whilst weaning or off steroids.

- Partial response

This refers to no progression of nonmeasurable lesions and no new lesions. Specifically, this is defined as $\geq 50\%$ decrease in sum of all products of diameters (SPD) of all target lesions with stable clinical symptomatology and a stable steroid dose.

- Progressive disease

This differs from partial response with having $\geq 25\%$ increase in the sum of target lesions, with significant increase in nonenhancing lesions, with clinical deterioration with no decrease in steroid dose and/or a new radiological lesion.

- Stable disease

This is the radiological diagnosis of exclusion of neither complete nor partial response, with lack of progression seen.

As per the RANO guidelines, criteria for progressive disease is met when the majority of new enhancement is noted beyond the 80% isodose line of radiotherapy or on histopathological confirmation. This is an important point for us to bear in mind, as a third of glioblastoma patients may be reported on as undergoing pseudoprogression, thus this term needs to be utilized in accordance with the RANO guidelines. Also of importance, is the pseudoresponse seen post-antiangiogenic therapy (anti-vascular endothelial growth) which decrease the permeability of the blood-brain barrier thereby decreasing the gadolinium enhancement [14]. Radiological surveillance with T2/FLAIR is sensitive in identifying vasogenic edema and used in combination with DWI is a increases the likelihood of identifying tumor burden [15]. An improvement in T2/FLAIR is associated with improved survival and decreased mortality, DWI remains an independent predictor of progression free survival at 6 months [12, 15].

RANO guidelines state that all radiological responses must persist for four weeks prior to be considered 'true' progression or response: this is the crux of the RANO guidelines.

5. Immunotherapy

Glioblastomas undertake a host of immunosuppressive mechanisms, resulting in challenges for the immunotherapeutic interventions [16]. In this subsection, we discuss the immunotherapy and the use and rationale of trials and their application.

Optimal antitumor therapy needs to have an antigen as an immunological target along with the activation of the immune system for facilitating trafficking and infiltration of the now activated immune system targeting the tumor.

Let us start by overviewing the multiple key immunosuppressive mechanisms existing within the highly plastic glioblastoma microenvironment. Regulatory T cells (Tregs) are produced within the thymus (nTregs) or are induced (iTregs). Of the two, nTregs are noted in higher concentration within the glioblastoma tumor clusters [16]. Immunosuppressive mechanisms have been directly correlated to, by identifying the cytokines within the tumor cysts fluid secreted by the Tregs: transforming growth factor beta [TGF- β] and interleukin 10 [IL-10]. Inhibitors of TGF- β receptor kinase are currently in preclinical testing. Up to a tenth of the

mass of glioblastomas consist of the tumor-associated macrophages (M2 lineage) and microglia. The aggressiveness of glioma-stem cells is enhanced by the secretion of TGF- β by the tumor-associated macrophages. The glioblastoma stem cells increase the number of circulating Tregs and also activate the signal transducer and activator of transcription 3 (STAT 3), which is found to be ubiquitously expressed in glioblastoma cells [16].

High-grade glioma progression has also been shown to be enhanced in the presence of glioma-secreted colony stimulating factor 1 (CSF-1) to cause polarization of tumors toward the glioma-supportive (M2) phenotype [17]. Of note, the vascular endothelial growth factor (VEGF) has multiple functions of tumorigenesis and simultaneously of inhibition of dendritic cell function. We discuss the role of anti-VEGR receptor agents in further detail below in subsection 6.

Immune checkpoint programmed death PD-1 binds the ligand for PD-1 (PD-L1) to suppress CD4+ and CD8+ cells. PD-L1 is upregulated in gliomas, specifically the mesenchymal subtype of glioblastomas and has been associated with inhibition and apoptosis of T cells. Anti-PD1 blockade has been undertaken in the murine glioblastoma models successfully with an increase in survival, in combination with radiotherapy [18].

Cytotoxic T-Lymphocyte-associated protein 4 (CTLA-4) is an inhibitory surface receptor found on constitutionally active Tregs, and hence, is the other immune checkpoint inhibitor of great clinical interest [19, 20]. The FDA has recently approved ipilimumab, a monoclonal antibody directed against CTLA-4, after Phase III trials for melanoma patients showed an objective increase in survival. In the murine model, anti-CTLA-4 and IL-12 administration demonstrated a reduction in Tregs and increased immune effector response, which is now under investigation for glioblastoma therapies [21, 22].

An investigational immunotherapeutic agent that has been in the limelight for the past couple of years is RINTEGA® (Rindopepmut CDX-110). RINTEGA® is administered intradermally and consists of the EGFRvIII-specific peptide sequence conjugated to keyhole limpet hemocyanin, thereby stimulating pronounced EGFRvIII-specific humoral and cellular responses resulting in the production of anti-EGFRvIII antibodies infiltrating and attacking the tumor. EGFRvIII is a tumor-specific oncogene and a mutated form of the epidermal growth factor receptor (EGFR), which is noted in one-third of all GBM cases with aggressive tumor proliferation and correspondingly poor median survival compared with other glioblastoma cases [23–25]. EGFRvIII is not expressed in normal tissue, hence making it a unique immunotherapeutic target.

Hence, at this point, we will dedicate a few lines to the discontinuation of the ACT IV study in March 2016 based on the recommendation of the Data Safety and Monitoring Board and an update has appeared on the Celldex Therapeutics website. ACT IV was a Phase III study conducted in newly diagnosed EGFRvIII-positive glioblastoma patients with RINTEGA® and granulocyte-macrophage colony stimulating factor added to standard of care temozolamide with the control arm regimen undergoing standard of care temozolamide plus intradermal keyhole limpet hemocyanin. The control arm significantly outperformed expectations (hazard ratio = 0.99; median OS: RINTEGA 20.4 months vs. control 21.1 months) and hence the study showed an inability to meet the primary outcome survival endpoint.

The ReACT study is the randomized, Phase II trial of RINTEGA® in combination with bevacizumab (Avastin®) in patients with recurrent EGFRvIII-positive glioblastoma. In November 2015, Celldex Therapeutics reported long-term survival data in group 1 (bevacizumab-naive patients randomized to receive either RINTEGA or a control injection of KLH in a blinded fashion; all patients also received bevacizumab) at the Society for Neuro-Oncology Annual Meeting. At two years, the survival rate was 25% for patients in the RINTEGA arm versus 0% for patients in the control arm, with continuing advantage shown across multiple endpoints [26].

6. Anti-angiogenic treatments

The pathological angiogenesis of glioblastomas is a hallmark of the disease process, with multiple mechanisms hypothesized, including the transdifferentiation of tumor cells into endothelial cells, vascular mimicry, and vessel co-opting [27]. Tumor angiogenesis has been shown to be associated with the recruitment of hematopoietic and circulating precursor cells [28].

The VEGF (vascular endothelial growth factor) pathway is highly expressed in glioma angiogenesis with overexpression of VEGF-A. There have been a multitude of factors identified to propagate and inhibit the VEGF pathway, including hypoxia inducible angiogenic factors, and endogenous factors like placenta growth factor. The anti-VEGF/VEGR compounds inhibit the proliferation of endothelial cells and neoangiogenesis, with a corresponding decrease in the permeability of the blood–brain barrier. Within 48 hours of anti-VEGF-A therapy with bevacizumab (Avastin®), there is decreased contrast enhancement, which may be misleading and hence to be read as a pseudoresponse. In contrast the T2/FLAIR progression is seen on serial radiological imaging, which has been postulated to be a nonangiogenic invasive growth pattern and the likelihood of T2 progress predicting subsequent T1 and in turn tumor progression [14, 29]. Hence, our above discussion on RANO criteria will be called upon here to be borne in mind while analysing the imaging characteristics of patients on antiangiogenic therapy.

Bevacizumab (Avastin®) is the antibody to VEGF-A which has been utilized in Phase I, II and III trials to investigate its role in both newly diagnosed and recurrent glioblastoma. Of note, the AVAglio (Avastin® in Glioblastoma) study was undertaken in a for newly diagnosed glioblastoma patients in a randomized manner (bevacizumab versus placebo) with double-blinding. Postsurgical resection, the patients were commenced on the Stupp protocol (concurrent radiotherapy 2 Gy 5 days a week and temozolomide 75 mg/kg) in combination with intravenous bevacizumab 10 mg/kg (or placebo) every fortnight. After a 28-day treatment break, the patients were commenced on a maintenance dose of temozolomide (150–200 mg/kg) and fortnightly intravenous bevacizumab (10 mg/kg) or placebo for 6 weeks. This was followed by bevacizumab (10 mg/kg) every three weeks as monotherapy. The patients were assessed clinically at predetermined, regular time points. The results of the AVAglio study echoed those of the Phase III Radiation Therapy Oncology Group (RTOG-0825) with

both studies showing a trend toward increase in progression free survival but no significant difference in overall survival [30, 31]. It is important to note, as with other previous studies, the adverse effects of the bevacizumab group were noted to be higher than in the placebo group and noted to include hypertension, proteinuria, and (arterial) thromboembolism. The question arises regarding the failure of progression-free survival to overall survival, and it is postulated there are possible escape mechanisms in the anti-VEGF pathway and treatment which results in an aggressive, recurrent tumor [29]. The crossover seen in the AVAglio trial may have had considerable impact on the true survival data, and in comparison the BELOB [single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma] Phase II trial had virtual exclusion of patient cross-over to the bevacizumab arm, and also surprisingly there were fewer of the above-described adverse effects of bevacizumab [8]. Additionally, while the predictive value of MGMT promoter methylation and treatment with temozolomide is well known [32], the prognostic significance in association with anti-angiogenic or other chemotherapeutic agents is less well understood. Thus, in increasingly more of the recent trials, the MGMT status is included and required to allow the study of temozolomide-free arms [29]. It has also been noted in preliminary clinical trial data that angiopoietin-1/-2 may potentially destabilize vessel and when used in association with VEGF-A, angiogenic synergy is exhibited and further clinical trials being undertaken with this hypothesis in mind [27].

Moreover, genetic expression data of glioblastoma subgroups has been recently retrospectively explored using the AVAglio trial data. To recap, the Cancer Genome Atlas subdivides the heterogeneous entity of glioblastoma into the following subtypes: proneural, classical, and mesenchymal (with the previously known neural subtype possibly being an artefact) [33]. In this most recent study, the addition of bevacizumab is shown to be associated with increased overall survival in the proneural subtype GBM, with naïve, nonmutated IDH [34]. This report came as a welcome surprise to the Neuro-Oncology community, as patients with the proneural subtype lacking IDH mutations have historically a poorer survival compared with proneural subtype with IDH mutations.

We also note that on preclinical GBM models, it has been shown that bevacizumab induces hypoxia in treated tumors, which is accompanied by increased glycolytic activity and tumor invasiveness [35]. This is an area for further research to exploit in view of anaerobic glycolytic dependency of glioblastomas and is discussed below in subsection 8 in further detail.

7. Glioma virus therapies

Glioma virus therapies are broadly divided into two categories. Replication-deficient viral vectors to be used as delivery vehicles for therapeutic, antitumor genes. Second, are the replication-competent oncolytic viruses that target, infect, and replicate within the host glioma cell with the intent of destroying the tumor host cells with progeny particle release [36, 37]. The two viruses studied most widely are the adenovirus and herpes simplex (HSV-1) virus. There are double-stranded DNA viruses, whereby extensive modification may be carried out

in order for the virus vectors to carry the therapeutic genes under investigation [36]. While there are multiple Phase I and II clinical trials underway (clinicaltrials.gov), an impetus remains on the parallel to streamline the efficacy of these viruses to ensure the potency of the viral vectors without overtly impairing the host immune system response (may want to note that the mechanism of some of these virus such as the Duke polio virus may be by immune system induction). Convection enhanced delivery using continuous, positive pressure bulk flow of the therapeutic virus to the glioma may be undertaken to improve delivery [38, 39]. Specificity may be enhanced for viral entry into the glioma on modification of attachment-mediating surface proteins and chimeric capsids [25]. Of most interest, are the viral genes being engineered to be enhanced using hypoxia-responsive promoters in areas of low-hypoxia, a known glioma phenotype [37, 39].

Of note is the Toca511 trial, with an estimated completion date of November 2017. This is a multicenter, randomized, Open label Phase II/III study of Toca 511 and Toca FC versus standard of care. This comprises investigator's choice of single-agent chemotherapy (lomustine or temozolomide) or bevacizumab administered to patients with recurrent high-grade gliomas. Toca 511 (vocimagene amiretrorepvec) is an investigational injectable retroviral replicating vector (RRV) encoding a yeast-derived prodrug activator enzyme, cytosine deaminase (CD). Toca 511 selectively infects and spreads through the high-grade glioma cells, thereby delivering the CD gene and the tumor cells can then produce the CD enzyme.

Toca FC is an orally administered, extended-release version of prodrug 5-fluorocytosine (5-FU) which is absorbed and carried through the bloodstream. This crosses the blood-brain barrier and is then converted by the CD enzyme into the active 5-FU, at high concentrations within the glioma cells infected by Toca 511. 5-FU in turn causes tumor cell apoptosis and activation of the immune system by the release of tumor-associated antigens and viral proteins from the dying cells. We look forward to the results of this retroviral replicating vector against high-grade gliomas and the possible extrapolation to other solid cancers.

8. Tumor treating fields

In 2015, Optune™ became the first FDA-approved therapy for newly diagnosed glioblastomas in over a decade to demonstrate statistically significant extension of progression free and overall survival. Optune™ is the brand name for the NovoTTF™ 100A system manufactured by the commercial stage oncology company Novocure™.

Optune™ is a portable, noninvasive device delivering low-intensity, intermediate frequency, alternating bidirectional electric fields referred to as Tumor Treating Fields (TTF). The electric fields are delivered locoregionally via transducer arrays through the shaved scalp. The mechanism of action is the antimetabolic action of the tumor treating fields interfering with cell division and organelle assembly within the rapidly replicating tumor cells. While microphotography has shown examples of prolonged mitoses and proliferation arrest, the specificity of the tumor treating fields for tumor cells only in the absence of an exact mechanism has raised skepticism within the Neuro-Oncology and Oncology clinician community [40].

What is undeniable, however, is the two-year survival rate among patients treated with Optune™ in combination with temozolomide was 48% higher than in patients compared with patients treated with temozolomide alone [41]. In 2014, the multinational, randomized Phase III EF-14 trial was halted after successful demonstration of superior progression-free and overall survivals in patients receiving Optune™ in combination with temozolomide, compared with temozolomide alone. Patients treated with Optune™, in combination with temozolomide, demonstrated a statistically significant increase in progression-free survival compared with temozolomide alone (median progression-free survival of 7.2 months compared with 4.0 months, hazard ratio = 0.62, $p = 0.001$). There was also a statistically significant increase in overall survival compared with temozolomide alone (median overall survival of 20.5 months compared with 15.6 months, hazard ratio = 0.66, $p = 0.004$) [40–42]. It is noted that patients in the control arm received a median of four cycles of temozolamide, whereas patients in the Optune™ arm received six cycles of temozolamide, which is an additional confounding factor (patients lived longer therefore they got more temo).

The bottom line here is the availability of Optune™ as a viable option for all patients with newly diagnosed glioblastoma after successful chemoradiation and stable disease at potential initiation of treatment with tumor treating fields [42]. We look forward to the incorporation of Optune™ in future trials as a standard arm and with permutations of other combinatorial therapies.

9. Glycolysis in glioblastomas

Glioblastomas appear to thrive and proliferate in a hypoxic environment, thus relying upon anaerobic glycolysis [43]. Thus research efforts over the past decade have been toward maximizing of glycolytic inhibition within the hypoxic glioma environment [44–47].

In their 2015 paper, Sanzey et al. undertook genome-wide transcriptomic analysis of patient-derived glioblastoma and stem cells to demonstrate a strong upregulation of glycolysis-related genes in response to severe hypoxia. Glioblastoma xenografts were used to identify seven glycolytic genes, with knockdown that led to a dramatic murine survival benefit, with phosphofructokinase-1 [PFK1] and pyruvate dehydrogenase kinase-1 [PDK1] as the most promising therapeutic targets to address the metabolic escape mechanisms of glioblastomas [44]. At this point, it is instructive to correlate the high glycolytic states of tumor cells to the increase in the radioresistance of glioblastomas [48]. A pyruvate dehydrogenase kinase inhibitor [Dichloroacetate] is used to treat lactic acidosis and is noted to modify tumor metabolism by activating mitochondrial activity and thus, force glycolytic tumor cells into oxidative phosphorylation. Dichloroacetate alone demonstrated modest antitumor effects in both in vitro and in vivo models of glioblastoma and reversed the radiotherapy-induced glycolytic shift, thereby improving the survival of orthotopic glioblastoma-bearing mice [46]. We look forward to clinical trials modulating the metabolic state of glioblastoma cells and thus, modify their sensitization to radiotherapy.

10. Conclusion

The past several decades have seen an explosion of information on the molecular biology of gliomas and immune environment of cancer. There have been a proliferation of trials involving novel signal transduction inhibitors, neoangiogenic, and immune modulatory targets. Novel methods of delivery of therapeutic molecules and genes have been developed, including a novel device to deliver nonionizing energy to inhibit mitosis. Imaging criteria have been developed to better assess response to therapy and aid the clinician and researcher in evaluating the tumor response to these diverse therapeutic modalities. New genetic testing has been developed in order to predict prognosis and will soon be incorporated into clinical trials as Neurooncology moves toward the goal of more personalized cancer therapy.

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