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Gliomatosis cerebri: a consensus summary report from the Second International Gliomatosis cerebri Group Meeting, June 22–23, 2017, Bethesda, USA

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Abstract

Gliomatosis cerebri (GC) is an aggressive glioma characterized by an invasive growth pattern and a dismal prognosis. The low incidence and non-specific symptoms at presentation pose unique challenges for early diagnosis and disease-specific research. There is no standard of care for the treatment of patients with a GC phenotype. Understanding the biology of this entity is a critical step in determining effective treatments. Toward this end, the Second International GC Group convened at National Institutes of Health, Bethesda on June 22nd–23rd 2017. This paper summarizes the main conclusions and recommendations for research priorities to fight this fatal condition.

Keywords

Gliomatosis cerebri; Meeting; Consensus; Second International Gliomatosis cerebri Meeting 2017

Introduction

Gliomatosis cerebri (GC) is currently recognized as an extremely infiltrative pattern of diffuse glioma spread, rather than a discrete histologic or molecular subtype of glioma. Traditionally, morphologic classification and grading of astrocytic tumors, including GC, has been established using histologic examination of tumor tissue including standard

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Compliance with ethical standards

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hematoxylin and eosin staining, immunohistochemistry, and more recently basic molecular characterization. However, the diagnosis of GC is controversial as there is no common consensus for the pathologic and radiographic description of GC. There is no clinical hallmark of GC and the prognosis is variable. Even in patients who have a histologic diagnosis of glioma, there is no standard radiographic criteria delineating a diagnosis of GC. Many diseases such as progressive multifocal leukoencephalopathy, Behcet's disease, viral encephalitis, vasculitis, subacute sclerosing panencephalitis can mimic the appearance of GC [1, 2]. Molecular studies on GC have demonstrated genetic alterations such as isocitrate dehydrogenase 1 (IDH) mutation, tumor protein 53 (TP53) mutations and epidermal growth factor overexpression which are not specific for GC and also found in other diffuse gliomas [3–5]. Subgroups defined by DNA methylation profiling are also similar to other gliomas [5]. Treatment of GC is challenged by the fact that there is no established standard of care in either the adult or pediatric population. The use of radiation therapy is difficult as the disease is often radioresistant and the radiation field is frequently large, leading to extensive neurotoxicities. Similarly the role of chemotherapy is not well-established, though patients have been treated with temozolomide and lomustine based regimens [6–8].

The World Health Organization (WHO) classification historically has been ambivalent about its stance on GC as a specific disease. In 1993, there was initial consideration as to whether it deserved inclusion as a distinct pathological entity [9]. In 2016, GC was eliminated as a distinct *pathologic* entity based on overlap of discrete molecular alterations with other high-grade gliomas, and the absence of distinct molecular or histologic features compared to other malignant gliomas [5, 10–12]. However, it was noted that GC merits further study as this phenotype has characteristic and unique migration and invasiveness patterns and different treatment outcomes. The First International Gliomatosis cerebri Group Meeting was held in Paris (France) in 2015 [13]. This meeting refined the diagnostic criteria of GC suggesting that rather than defining GC based on a radiologic definition, this entity should be recognized as diffuse gliomas characterized by similar infiltrative spread and aggressive clinical course. Experts focused on appropriate diagnostic procedures such as use of magnetic resonance (MR) imaging and MR spectroscopy and recommended that at least two different biopsy samples be obtained using the same needle tract at different tumor depth to reduce sampling error. A major initiative was the establishment of GC registries in the United States (New York) and Europe (London and Heidelberg) with a goal to extensively study the molecular profile of GC cases. In 2017, a dedicated group of scientists and physicians met in Bethesda, USA with GC families and foundations from around the world for the Second International Gliomatosis cerebri Group Meeting. The meeting focus was to review the progress made towards the understanding of GC and to develop meaningful collaborative projects to be implemented within the next two years. Three provocative projects were identified: (1) sequencing and target identification, (2) evaluating the potential of immunotherapy, and (3) clinical translation.

GC affects all age groups, although appears to be more prevalent in adults [2]. Although most epidemiologic studies are small, the median age at diagnosis has been reported from 37 to 66 years and it shows a slight male predominance [2, 14–16]. Patients can present with seizures, symptoms of raised intracranial pressure, cognitive changes and motor deficits. The

diagnosis of GC is reached with a combination of clinical symptoms, radiographic criteria and histologic confirmation. Brain MR imaging shows diffuse T2 FLAIR white matter involvement in more than two contiguous lobes or areas of the brain. Classically, no significant contrast enhancement is present. Pathological examination of the tumor tissue shows a predominantly astrocytic tumor, which can be grade II, III or IV. Oligodendroglial phenotype is less common. Unfortunately, in many cases, there is no tissue confirmation of tumor, limiting the availability of samples for research. In a recent Surveillance, Epidemiology and End Results study on adult GC patients, from 1999 to 2010, only 58% of patients had a documented pathologic confirmation of GC [14]. In terms of clinical management, there is no general agreement on therapy. Many centers treat these patients as malignant glioma, with radiation therapy and chemotherapy, although this is difficult to assess as diagnosis may be recorded as glioma, malignant glioma or glioma, not otherwise specified. Additionally, most patients with GC are excluded from clinical trials for adult highgrade glioma. Median overall survival (OS) is reported ranging from 7 to 18.5 months [2, 14, 15, 17]. The GC International Registry, New York reported an OS of 17 months in children and found that age > 10 years, male gender, and lowgrade pathology favored a longer OS [17]. A consensus paper including diagnosis and treatment recommendations in pediatrics was published in 2016 [13].

Recent Gliomatosis cerebri progress

It is not surprising that recent DNA methylation profiling data demonstrates that adult and pediatric GC clusters with other well recognized glioma molecular sub-groups and do not express specific molecular markers [5, 10]. Subsequently, the revised 2016 WHO classification for central nervous system (CNS) tumors removed GC as a distinct histopathological entity [11]. More extensive analyses of GC samples will further address glioma sub-categorization of GC patients, including determination as to whether some groups are enriched or if new categories are identified. The European Society for Pediatric Oncology (SIOPE) highgrade glioma/ diffuse intrinsic pontine glioma (DIPG)/GC brain tumor working group is in the process of retrospectively collecting and centrally reviewing radiologic and histopathologic features of GC cases across European countries, which may provide answers and insight into GC subgrouping. In the United States, a GC International Registry is currently located in at the Weil Cornell Medical Center, New York. It collects clinical data and tissue samples of patients with GC. Patients or their family member may seek to enroll in the registry which serves as a central repository and uses the collected tissue samples for genomic sequencing. The invasive and migratory biology of GC needs to be understood and meaningful research projects may unveil key mechanisms for tumor initiation, maintenance and progression. Outstanding key questions that need to be addressed include what makes these glioma cells so infiltrative? What gives them the capacity to migrate throughout the brain in short periods of time? What is the interaction of tumor cells with the brain microenvironment and the periventricular neural stem cells? Why do they preferentially invade rather than form a distinct tumor mass?

Dedicated laboratories in North America and Europe have established several GC cell lines, enabling disease-specific pre-clinical studies and potential development of animal models. Ongoing molecular and functional studies designed to better understand the biology of this

disease will hopefully lead to identification of disease-specific targets and more effective therapies. Gliomas of corresponding grades and pathology will be used as comparison groups for biologic, molecular and other investigations of GC cases. In an effort to obtain statistically significant findings for this rare disease phenotype, there is a proposal to establish a SIOPE registry for the centralized study of GC cases across Europe.

Relevant current clinical trials for GC, the National Institutes of Health (NIH) initiative

The NIH is developing a natural history and biology study of children, adolescents and adults with GC. This natural history study is envisioned as a comprehensive study, enrolling GC patients at any point in their disease course. It aims to develop a better understanding of GC natural history and elucidate its biology and pathophysiology by extensive tumor profiling. Tumor tissue will be assessed longitudinally, at initial diagnosis and at the time of progression. Samples will be interrogated for genomic analysis, methylomics and evaluation of the tumor microenvironment. Clinical assessment is , audiology, endocrinology, and neuro-psychiatry, as well as patient reported measures including quality- of-life assessments. Multi-parametric imaging with diffusion tensor imaging, diffusion weighted imaging, MR spectroscopy and 18F-fludeoxyglucose positron emission tomography (PET) will be incorporated to study tumor invasiveness, grading and metabolism.

The Neuro -Oncology Branch at NIH, currently has an open phase II trial (NCT03173950) of the immune check-point inhibitor, nivolumab, in patients with select rare CNS cancers and includes GC. This trial will provide an opportunity to study correlative GC biology, immune expression, subtyping of tumor infiltrating lymphocytes, and evaluate any relationship between pretreatment immunocompetence and phenotyping correlates with response to nivolumab.

Provocative projects

One goal of this meeting was to identify three provocative projects specific for GC and define objectives and action items for each. A 2-year timeline is targeted for each of the provocative projects.

Project 1:

Focused on GC tissue sequencing and target identification. For a comprehensive study on GC biology, there was a consensus for creating an international GC registry similar to the existing DIPG registries in North America (<http://www.dipgregistry.org>) and Europe (SIOPE DIPG Registry). As GC is heterogeneous, often with a solid and an infiltrative portion, experts recommended that tumor tissue should be sampled from more than one site, with emphasis on tissue sample from any solid tumor component or central tumor as well as infiltrative part.

Project 2:

Focused on the evaluation of the potential of immunotherapeutics for patients with GC, particularly given the exceptional response of a patient with GC on a Phase 1 study of radiation therapy administered with the immunomodulatory agent, lenalidomide [18]. There are multiple unknowns in this patient population including baseline immune function, immunosuppressive mechanisms in the tumor microenvironment and if this differs from those with other malignant glioma phenotypes, and presence or absence of tumor-specific antigens. To identify target antigens, tumor samples need to be studied genetically with single cell RNA sequencing and the exploration of tumor microenvironment. Several studies have described a synergistic effect of radiation therapy with immunotherapy and this opportunity should be explored in GC [19, 20]. Projects on immuno-therapy should be linked to the GC registry so that tumor tissue and response to immunotherapy can be systematically studied.

Project 3:

Focused on clinical translation of GC-specific pre-clinical and patient-related research. However, due to the lack of understanding of the biology in GC, experts agreed that initial studies should focus on preclinical studies on GC invasiveness, with clinical studies subsequently projected to be built upon this work. Meeting attendees proposed and supported multiple biopsies (solid or tumor interior versus invasive edge) when possible at diagnosis [6]. The group also recommended serial cerebrospinal fluid and serum sampling, and novel imaging techniques (i.e. 18F-dihydroxyphenylalanine PET) to evaluate response to treatment.

The way forward

Although GC is no longer identified as a discrete histologic glioma subtype, it remains a unique pathological process with rapidly malignant course. No mutational signature of GC has been found. It is plausible that GC is a type of convergent evolution of various diffuse gliomas, by which they escape tumor cell killing. Efforts are needed in other spheres such as study of tumor microenvironment, single cell RNA sequencing, proteomics and immune function to unveil the mechanism of invasiveness in GC. Development of a comprehensive international GC registry to study the GC biology, further research into exploring immunotherapy for GC and investing into GC pre-clinical studies will pave a way forward into improving our understanding and translating GC research to patient care.

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