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# GLIOMATOSIS CEREBRI: A REVIEW

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## OPINION STATEMENT

Gliomatosis cerebri (GC) is an intriguing disease for several reasons. First, it is almost impossible to draw the border between GC and diffuse gliomas. In this regard, GC could represent the most invasive form of diffuse gliomas. Second, both in terms of histological grading and clinical course, GC is a heterogeneous disease, ranging from rapidly evolving to slowly and somewhat indolent forms.

Because of the extensive spread of the disease, surgery –outside a biopsy for diagnosis- is rarely indicated in gliomatosis cerebri. Therapeutic options include radiotherapy, generally involving the whole brain, and chemotherapy with temozolomide or nitrosoureas. Due to the rarity of the disease, no trial comparing these two modalities has been undertaken so far. Decision is therefore based on small retrospective non comparative studies and expert opinions. On one hand there is a rationale to postpone the whole brain radiotherapy because of late neurotoxicity, but on the other hand there is also the risk that an aggressive disease evolves to intracranial hypertension making the radiotherapy hazardous or even impossible. As a consequence the patient would lose the opportunity to receive a potentially effective treatment. In this decision, the evaluation of histological data

together with clinical and radiological features, performance status, and molecular profile may be of help.
Because radiotherapy usually involves large volumes of the brain, chemotherapy is generally preferred up-front in patients with a slowly evolving disease. Conversely, in patients with rapidly (ie over few weeks) evolving disease with neurological deficits or when histological features of glioblastoma are evident, whole brain radiotherapy (45 Gy with 1.8 Gy fractions), alone or associated with concomitant temozolomide, is often preferred.
The value of advanced MRI and PET techniques to predict outcome and monitoring the treatment still remains to be defined.

## INTRODUCTION

*Definition*

According to WHO 2007, gliomatosis cerebri (GC) is defined as "diffuse glioma, usually astrocytic, growth pattern consisting of exceptionally extensive infiltration of a large region of the CNS with the involvement of at least three cerebral lobes, usually with bilateral involvement of the cerebral hemispheres and/or grey matter, and frequent extension to the brain stem, cerebellum and even the spinal cord". In addition, an oligodendroglial phenotype can be present. GC is considered as a grade III tumor by WHO classification.
GC includes "de novo" gliomatosis (primary gliomatosis); conversely, the term "secondary gliomatosis" refers to a diffuse pattern of growth of a preexistent focal glioma.
GC has been for a long time considered as a rare and very aggressive tumor, with most cases diagnosed at autopsy[1]. The widespread use of MRI clearly shows that the incidence has been underestimated in the past and also reveals a wide heterogeneity in the outcome with a substantial number of indolent and slowly evolving cases. GC has been reported at any age (from infant to elderly patients, but clearly neonatal forms correspond to a different entity), with a peak incidence between 40-50 years and a slightly higher prevalence in males[2-5].
Because of the rarity of the disease, the majority of the publications are small retrospective case series or case reports: thus, many aspects of the disease remain to be clarified.

*Clinical aspects*

Clinical presentation is variable, depending on the structures involved. In the most recent series, seizures were more common than focal neurological deficit and intracranial hypertension[5-8]. When isolated, seizures often reveal a slowly evolving GC. In some patients the presentation consists of a status epilepticus. In contrast, older studies (including patients mainly from the CT-era) have indicated headache and intracranial hypertension as the most common presenting symptoms corresponding usually to aggressive and rapidly evolving GC [9-11]. GC can be revealed by isolated neurocognitive deficits and personality changes mimicking dementia [12] or by gait disturbance, cerebellar signs, cranial nerve palsies in case of an infratentorial involvement. GC can be revealed by unusual symptoms such as Parkinsonian syndrome when involving basal ganglia [13], blurred vision due to optic nerve infiltration [14] or spinal symptoms in case of spinal cord involvement.

*Neuroimaging*

CT shows only subtle ill-defined low density or even isodensity diffuse brain swelling, discrete ventricular asymmetry, but it does not adequately reveal the true extent of the disease, and may even be considered normal in a minority of cases[4]. MRI has a greater sensitivity, showing diffuse T2/FLAIR hyperintensities of the involved cerebral structures; mass effect may be absent or minimal, while in up to one third of patients small and patchy areas of contrast enhancement are present. Such features are non-specific and patients are often misdiagnosed with other neurological diseases, such as CNS inflammatory diseases, vasculitis, encephalitis, leucoencephalopathies, especially when there is no obvious mass effect[4]. Nevertheless, asymmetrical or heterogeneous distribution of hyper-intense areas on FLAIR/T2 sequences, mild hemispheric swelling, collapse of a ventricular horn, thickening of the corpus callosum, involvement of the anterior white commissure, loss of clear delineation between white and gray matter are all suggestive of GC [11,15-19]. Most of the GC predominate in the white matter; less frequently GC involves predominantly grey matter and shows an abnormally thick cortex or bilateral involvement of basal nuclei and thalamus[19] (Figure 1). During the course of the disease, another third of patients develop contrast-enhancing lesions, sometimes with important mass effect.

Advanced neuroimaging can be of help to manage patients with GC. Compared with low grade gliomas (whose MRI pattern can be similar), GC often displays lower choline levels and higher myoinositol and creatine levels [20-22]. Metabolic abnormalities may be detected in unaffected areas of the brain [23]. Diffusion

tensor imaging may visualize the relationships between fiber tracts and the infiltrating tumor [24] or appreciate the integrity of the white matter structure [25]. Cerebral blood volume is usually normal in GC [26], while PET with aminoacids may show focal hypermetabolism [27].

*Diagnosis*

GC simulates a wide range of diseases [4,28]. Due to the relatively low specificity of MRI findings, histological confirmation is mandatory, and shows a glial proliferation invading an otherwise normal brain parenchyma (Figure 1). Identification of tumor cells may be difficult, and immunohistochemistry may be very useful by showing a proliferating population with elevated Ki67 (Figure 1), and by identifying, in case of IDH1 mutated GC, single positive cells [29] (Figure 1). However, one must keep in mind that the biopsy may undergraduate the glioma aggressiveness, and this is particularly true in the case of GC. Therefore, the histological grading must be matched with clinical and radiological features.

*Prognostic factors*

Some studies, mostly retrospective, have tried to define clinical and molecular factors predicting the outcome.

Better outcome is associated with low grade histology, young age and good performance status[4,7,30,31]. It is also likely that patients with oligodendroglial phenotype, 1p19q codeletion, MGMT promoter methylation and IDH1 mutation have a better survival and better response to chemotherapy[29-31]. GC with prominent white matter involvement seems also to display a better outcome and higher response to chemotherapy: these cases have also a better performance status and are more frequently oligodendroglial tumors with 1p19q codeletion[19]. Conversely, grey matter gliomatosis is characterized in children by a very poor survival [32]. However, these data need to be confirmed by independent studies. Contrast enhancement was not consistently associated with outcome [7, 31].

MRS could be used as a predictor of response to therapy or of progression [33-35]). The choline/creatine index on MRS has been reported to inversely correlate with survival [36].

**TREATMENT**

There is no standard treatment for GC, and the therapeutic choice should be tailored to the patient characteristics. In addition, GC is an extremely heterogeneous entity, and the indications are based on small retrospective non comparative studies, case reports and experts opinion, ie a low level of evidence (class IV). An additional difficulty is due to the fact that biopsy may underestimate tumor aggressiveness: therefore, the histology must be matched with clinical and radiological data. Although there is no indication on the respective efficacy of chemotherapy vs radiotherapy, all data suggest that both regimens are effective up-front in GC. This prompted several groups to propose chemotherapy as up-front treatment

*Surgery*

Given the extensive spread of the disease, patients with GC are rarely offered surgery outside of diagnostic purposes. In some cases a surgical decompression is needed to relieve local mass effect. There are no data evaluating the impact of surgery in GC both at the time of diagnosis or at recurrence. A retrospective study found no significant advantage both in terms of disease progression and overall survival for partial resection compared to biopsy[37] .

Radiotherapy

Radiotherapy (RT) has been for long time the treatment of choice of GC. Available data are based on small retrospective and heterogeneous studies in terms of inclusion criteria.

Cozad et al. (1996) published 3 cases treated with RT, with no clinical or radiologic benefit[38]. Elshaikh et al (2002) reported a median survival of 11.4 months in 8 patients treated with RT alone (median dose 55.4 Gy) with a clinical response in 3 patients[39].

A series of 30 GC, patients were treated from 1980 to 1998 at MD Anderson with localized (22 patients) or whole-brain (8 patients) radiotherapy (median dose 54.9 Gy; range 50-66 Gy): clinical improvement was observed in 70% and radiological partial response in 33% of patients, median PFS was 10 months and median OS 18 months[37]. Twenty-two patients were treated at University of California from 1990 to 2000: median OS was 28 months for patients treated with RT alone [31].

A retrospective review comparing patients receiving radiotherapy with patients not receiving radiotherapy did not reveal a prolongation of survival for the radiotherapy group [4]. Moreover, the survival after salvage radiotherapy in patients failing primary chemotherapy is only of few months [40]. In contrast, a series of 54 patients from the Mayo Clinic found radiotherapy strongly associated with better prognosis, but selection bias could be present in this retrospective study [41].

*Chemotherapy*

In the last years chemotherapy has been increasingly used as initial treatment with the aim to postpone large field radiotherapy that may result in a non negligeable risk of neurotoxicity in long surviving patients.

The studies employing chemotherapy as upfront treatment are reported in Table 1.

In the early studies the PCV (Procarbazine-CCNU-Vincristine) regimen was the most used, and has been then replaced by temozolomide: the latter is better tolerated and can be delivered for long periods (2 years or more), whereas lung toxicity limits the use of CCNU to one year treatment. Nevertheless, the efficacy of PCV seems at least equal to TMZ[7,42]. A recent study performed in low grade gliomas found a prolonged decrease of tumor volume during a median time of 3 years after the end of the PCV regimen [43,44].

With PCV, Herrlinger et al (2002) reported a stabilization lasting 6 months in 4/6 patients[45]. Glas et al (2008) observed a median progression-free survival of 16 months and a median overall survival of 37 months among 12 patients[8].

Among the 17 patients treated with PCV in the ANOCEF study [7], objective clinical improvement was observed in 41% and a radiologic response (partial and minor response) in 31.2%, versus 30.5% and 24% for the 45 patients treated with temozolomide. Importantly, the response was often delayed occurring after 3 to 9 months and was maximal at 6 to 18 months after the start of treatment. No significant difference was seen between PCV-treated and TMZ-treated patients in either PFS (15.8 months vs 16 months) or OS (25.6 months vs 26.4 months). The PFS and OS were significantly longer for oligodendroglial tumors (21.2 and 33.9 months) than for mixed and astrocytic tumors (6.2 and 11.1 months).

In a retrospective compilation of published GC cases, the use of chemotherapy (mainly PCV) was associated with better survival, but again this may reflect a

population bias. The median survival of chemotherapy-treated patients varied from 11 months for astrocytic and mixed tumors to 36 months for oligodendroglial tumors[4].
Patients with 1p/19q codeletion had a higher response rate (88% vs 25%), higher PFS (24.5 vs 13.7 months) and overall survival (66.8 vs 15.2 months). Similarly, patients with unmethylated MGMT promoter tended to have a shorter PFS and a higher rate of progressive disease [30].
Levin et al (2004) treated with TMZ 11 patients and documented an objective response in 45%, a median time to tumor progression of 13 months and a progression-free survival of 55% at 12 month[3]. In a case series of elderly patients (aged 70-83 years) temozolomide yielded an encouraging survival of 16 months[46].
A retrospective AINO study [47] has compared in 51 patients the use of temozolomide in the upfront setting or at recurrence, respectively. Responses were similar for patients treated upfront (24.5%) or at recurrence (22.7%), and prevailed among patients with 1p/19q codeletion (55.5% vs 12.5%). A significant clinical improvement was observed in 31-33% of patients. Overall survival of whole series was 15 months.
The efficacy of primary PC chemotherapy has been recently confirmed in a prospective phase II trial by the German group (NOA-5), that has reported a failure-free survival at 8 months (primary end-point) of 50.3%, a median PFS of 14 months and a median OS of 30 months[40].
A recent retrospective study found a benefit for adjuvant chemotherapy (PCV or BCNU) after radiotherapy (24 months compared with 13 months for radiotherapy alone)[48].
The data on the combination of radiotherapy and chemotherapy are scarce[49]. A recent review on 61 patients, collected from the literature, found no differences in the rate of response between TMZ alone (26.2%), WBRT alone (26.2%) and concomitant TMZ and WBRT (20%)[50].

Considering the risk of late neurotoxicity with radiotherapy, we recommend to use up-front chemotherapy in the majority of the GC. GC with areas of glioblastoma should be treated with radiotherapy (with reduced dose owing to the large volume) combined with temozolomide[51]. Considering that the biopsy may underestimate the real grade of the tumor, radiotherapy possibly with temozolomide may be applied to clinically aggressive GC. In the attempt to propose a more aggressive treatment and to postpone the radiotherapy, an ongoing phase II trial performed by

AINO investigates the role of dose-intensification of temozolomide in primary gliomatosis cerebri.

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**Legend to the figure:**

A- An example of a grey matter GC involving mostly basal ganglia (top: T1 with gadolinium; Bottom: Flair). B- An example of white matter gliomatosis cerebri with excellent response to temozolomide (top: before treatment; bottom, after three temozolomide cycles, FLAIR). C- HE of a GC invading the corpus callosum. D- Ki67 labelling of the same sample. E- Ki67 labelling showing proliferating tumor cells invading the cerebellum. D- IDH1R132H labelling (Courtesy of Dr Karima Mokhtari)