Diagnosis and Treatment of Glioma in Adult: Chilean Consensus.

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Brain tumors are characterized by high morbidity and mortality. The vast majority are secondary tumors (metastasis). On the other hand, gliomas represent a 30% of primary tumors of the central nervous system. In the US, between 2007-2011, an approximate incidence of 21.4 cases every 100,000 inhabitants was estimated. Recent advances in the molecular biology of these tumors have made possible to substantially improve their classification, thus allowing a better correlation with clinical outcomes and prognosis. Along these lines, today it is possible to rank patients by risk and deliver treatments capable of extending global survival, between 5 to 7 years, for grade II and III gliomas. This consensus was prepared by a multidisciplinary panel of experts, coming from various Chilean Scientific Societies; therefore, involving all medical/surgical therapy specialties. Enlightened from molecular oncology, this proposal offers a clinically useful input which, along with an updated treatment/ follow-up review of these patients, allows us to understand the relevance of these biomarkers for an accurate disease management. It should be noted that this paper was prepared by the same team who prepared the Clinical Protocol for Adult Gliomas, in 2019, to be later published by the Ministry of Health, and that differs from it, which offers clinical-operative details, such as flowcharts and dose, our review attempts to reveal imaging and molecular advances and how they impact current management of the disease.

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1.- GENERAL CONSIDERATIONS

Brain gliomas represent 30% of primary tumors of the central nervous system (SNC)1. During the last few years, its incidence has been increasing and has become a severe sanitary issue, due to the horrible vital prognosis in high grade lesions and the big impact on quality of life in lower grade lesions. A recent analysis of the SEER Record (Surveillance, Epidemiology and End Results) reported a lower incidence of gliomas in Latin population, with a higher life expectancy from 1 to 5 years, despite the low access to therapies2. Local data on encephalon cancer (CIE-OR 70-72) are old (from 2003 to 2007) and report a general adjusted incidence rate per age (TAI) of 1.8 per 100,000 inhabitants for men and 2 for women 3. In regions, it calls out attention that; Antofagasta (4.6, men), Biobío and Valdivia (4.1, men) and 3.6 for women in the 3 aforementioned regions3. Regarding mortality, the most recent data (2016), regarding the group of "Encephalon and SNC" tumors, report 485 cases per year, due to this cause. 265 of them, are men and 220 are women4. It is important to highlight that there is a low percentage (50%) of histological confirmation for malignant brain tumors3. A series, coming from a local Hospital, reported a life expectancy of 6 months5 for glioblastoma (GBM), which is lower than usual life expectancy, close to 16 months6.

From a clinical standpoint, these patients have progressive or persistent cephalea, epileptic crisis, focal symptoms, such as language/gait/visual disorders and cognitive disorders with a subacute onset. In some cases, the disease is inquired as a finding.

Next, a review is presented, mainly focused on diagnosis progress (at an imagery and molecular level), and how this has achieved reorganization and optimization treatment of these patients, especially for carriers of WHO grade II, III and IV diffused gliomas (in adults). It is important to highlight that technical details and daily clinical performance, as well as surgical techniques, dosage and operational flowcharts may be reviewed in the Clinical Protocol of Adult´s Gliomas (Protocolo Clínico de Gliomas de Adulto), published by the Ministry of Health, in September 20197.

2.- IMAGERY DIAGNOSIS

The preferred imagery analysis is brain magnetic resonance (BMR), whose procedure should include the axial acquisition of the T2, FLAIR, diffusion, T2 GRE sequences or another magnetic susceptibility sequence (SWI), T1 SE with/with no Gadolinium contrast. The T2 FLAIR and T1 GAD sequences are the most used for determining infiltrative/increased uptake8 tumor component. Diffusion has a role to identify the hyper cellular tumor area. Magnetic susceptibility sequences allow to determine the intratumoral hemorrhage and the presence of calcifications[8].

Among the leading edge (BMR) techniques, perfusion by T2* (DSC) dynamic susceptibility contrast is the one most useful by using relative cerebral blood volume rCBV. It has a cutoff point of 1.75, thus allowing to differentiate low/high grade gliomas, with a sensitivity of 95% and a specificity of 70%[9].

Spectroscopy usefulness is low, as it is not specific enough to differentiate between tumoral and non tumoral pathology. Even though the correlation between choline/N-acetyl aspartate and choline/creatine could contribute in tumor gradation of gliomas, perfusion techniques are still the first choice in diagnosis[10,11].

3.- SURGERY

It is recommended to perform a wider surgery, as long as there are no high risks of permanent functional alteration, considering the stereotactic biopsy in the following cases; doubt about the diagnosis regarding pathologies not getting benefits from surgical treatment, such as brain lymphoma, in extended tumors with a significant non-dryable component, thalamic tumors, in patients with a poor functional condition (Karnofsky <70%) or in patients who reject exeresis surgery[19,20].

In case of brainstem stereotactic biopsies, the best scenario is to perform them with a software aimed to plan the pathway of the biopsy cannula, in order to minimize complications[18]. The choice between exeresis surgery or stereotactic biopsy should be taken by an oncological committee, on a cases-by-case basis.

4.- HISTOPATHOLOGICAL/MOLLECULAR DIAGNOSIS

Classification of primary WHO 201612 SNC tumors, was included into the WHO gradation I-IV, molecular biomarkers (biological behavior of the disease) as an accuracy strategy, aimed to optimize treatment and comprehension of the clinical prognosis thereof.

Under this paradigm, Table 1 summarizes the main biomarkers, the population suggested to study them, and the chosen techniques[12,13, 14.]

Regarding previous Table # 1, it is important to highlight the following 5 statements:

- Any gliomas reported in people older than 55 years old should have a IDH1& Ki67 analysis, by IHC.
- For Gliomas Grade II, III or GBM for < 55 years old with native IDH1, by IHC, our suggestion is to study them by means of PCR or GS for IDH 1/2, in order to discard undetectable mutations by IHC.
- Before any inconclusive histology of a GBM with very high Ki67 and negative IHC of IDH1, PCR or GS should be considered for IDH1 and IDH2.
- For tumors with disagreeing studies or those where it is not possible to perform biomarkers, the acronyms NOS is used (not otherwise specified).
- BRAFV600E is an infrequent mutation and its determination should be consi16dered on a cases-by-case basis, before any potential use of specific therapy under study.

5.- TREATMENT

5.1.- Surgery

Next, the main surgical considerations for two big groups of tumors, grade II diffused glioma and then, grade II-IV gliomas are described.

A.- Grade II, diffused gliomas

In diffused grade II WHO gliomas, surgery plays a fundamental role in the treatment, thus increasing progression free survival, general life expectancy and it probably reduces the risk of anaplastic transformation[15]. In general terms, a full surgery is recommended, as long as risks of permanent functional alteration are not increased.

For surgical planning, in tumors located in eloquent areas, advanced (BMR) techniques, such as functional (BMR) and tractography may be used. Awake surgery and intraoperative brain mapping must be considered as well for those tumors located in more critical areas (for instance, language-related areas). Neurophysiological intraoperative monitoring is suggested for tumors located within the motor area[16].

The exeresis degree will depend on the proximity or on the infiltration of the eloquent cortical/subcortical areas. In these tumors, which usually do not have contrast uptake, the resection objective is to cover all the area reporting hyper intensity in a T2 FLAIR sequence[17].

B.- Gliomas Grade III and IV

Mass resection will be applied for reported contrast uptake in (BMR) (T1 with GAD) and necrotic lesions. The same considerations must be taken into account for preserving the eloquent area, by using awake surgery and electrophysiological monitoring, when necessary.

6.- RADIOCHEMOTHERAPY (RT-QT)

6.1.- Gliomas Grade II (Astrocytoma and Oligodendroglioma)

6.1.1.- First line MUTED IDH

In terms of clinical risk, the following risk types appear in this classification:

- Low risk – for those patients younger than 40 years old, with full/nearly full exeresis and mutated IDH 1 or 2. Observation and follow up with periodic (BMR) 21 is suggested.
- High risk - for those patients younger than 40 years with biopsy or partial resection; patients who are 40 years old or older, regardless of the tumor resection degree; low risk WHO II gliomas, with tumor progression or gliomas Grade II NOS. Starting sequential RT-QT with Procarbazine, Lomustine and Vincristine (PCV), Procarbazine and Lomustine (PC) or Temozolomide[21,22] is suggested.

This behavior is based on the results from the study RTOG 9802, reporting extended global

Table 1. Addressing Gliomas in Adults, based on Personalized Accurate Oncology (OPP)

Biomarker	Objective Population	Suggested Diagnosis Techniques	Observations
Isocitrate dehydrogenase 1 and 2 (IDH 1 and 2) and substitution R132H of the IDH1	Basal Study for all gliomas grade II, and beyond	IHC, PCRo NGD	R132H is present in 90% of tall cases (IHC)
Mutation K27M of the Histone H3	Basal Study for all gliomas grade II, and beyond	IHC or GS	Its presence is associated to worse prognosis (life expectancy lower than 10%, at 2 years). It is an infrequent mutation.
Co-deletion 1p19q	Basal Study for all gliomas grade II, and beyond	FISH or PCR	Those with Oligodendroglial Morphology, with preserved ATRX, and with no overexpression of p53.
Expression of ATRX	Diffused gliomas older than 15 and younger than 55 years old	IHC	Widely used Techniques
Expression of p53			
Expression of Ki67			

Abbreviations: IHC: immunohistochemistry; GS Genome Sequencing; PCR: Polymerase Chain Reaction; FISH: Fluorescence in situ hybridization; ATRX: X-linked alpha-thalassemia/mental retardation syndrome.

life expectancy (SG) of 5.5 years, in absolute terms (13.3 years of SG with sequential RT-QT versus 7.8 years in the RT group)21. High PCV toxicity has made that many centers perform sequential RT-QT with Temozolomide as a first choice drug. Given the shallow penetration of Vincristine in SNC and its associated toxicity, some centers prefer PC treatment. Some retrospective evidence reports results comparable to the scheme with PCV[23].

Treatment with (RT or QT) monotherapy was reviewed by the work EORTC/NCIC-CTG/RTOG/MRC-CTU (EORTC 22033-26033 stage III)[24], reporting a progression free survival (PFS) for patients with mutation of IDH and co-deletion 1p/19q of 5 years. Exclusive QT may be considered for young patients, given the cognitive toxicity that is well reported for RT in the long term. However, patients treated with Sequential RT-QT have more than double progression free life expectancy[22].

5.1.2.- First line native IDH

Given the poor prognosis of this group (progression free survival with monotherapy in the work EORTC 22033-26033 was of only from 19 to 23 months). The discussion is if therapeutical monotherapy alternatives (RT or QT) or sequential RT-QT are enough; therefore, a more aggressive treatment is needed, such as RT-QT, according to Stupp´s Protocol6, similar to GBM treatment. However, this therapeutical choice is not reviewed in stage III studies; therefore, the suggestion is to evaluate this situa-

tion on a cases-by-case basis, according to the criterion of each center and its relevant oncological committee[21].

Second line

Before progression, management will depend on first line treatment received, and it involves evaluation, reoperation, re-irradiation and/or use of alkylant agents (Temozolomide/PC or PCV)[21]. Repetition of the scheme previously used, if progression occurs after 5 months since the previous treatment was completed or else to change the scheme[23] may be considered. In low grade native IDH gliomas Lomustine may be used thus homologizing GBM treatment[24].

6.2.- Anaplastic Gliomas, WHO Grade III (Astrocytomas or Oligodendrogliomas)

6.2.1.- First line, for Gliomas Grade III with IDH 1 or 2 mutated and co-deletion 1p/19q present or NOS Anaplastic Oligodendroglioma

The suggestion is Sequential RT-QT with PCV, PC or Temozolomide

This is based on results of 2 prospective/randomized/multicentric works that evaluated RT treatment versus sequential RT-QT with PCV, QT post-RT (EORTC 26951) scheme and QT pre RT (RTOG 9402)[27 28]. Both found benefit in the two sequential schemes when compared with exclusive RT for those patients with co-deletion 1p/19q and mutated IDH. If we take into account RTOG work, patients with co-deletion 1p/19q the combined therapy, improved SG in more than 7 years old (it duplicates medial SG: 14.7 years versus 7.3 years) and progression free survival (PFS) (8.4 years versus 2.9 years) when compared with RT; in patients with no co-deletion, but with mutated IDH. Benefits are observed in SG as well (5.5 versus 3.3 years)[27].

6.2.2.- First line, for Grade III Gliomas with IDH 1 or 2 mutated, and with no co-deletion 1p19q.

- The suggestion is Sequential RT-QT, with PCV/PC/Temozolomide.
- The suggestion is RT-QT, concomitant and adjuvant with Temozolomide (Stupp´s Protocol).

The CATNON study is a stage III multicentric study on Anaplastic Gliomas, with no co-deletion 1p19q. It randomized patients in 4 branches: RT with 59.4 Gy, with/with no 12 adjuvant cycles of Temozolomide and concomitant RTQT with/with no 12 adjuvant cycles of Temozolomide. The first report grouped the therapies, according to randomization or not to QT adjuvant. A significant benefit was reported in PFS in patients who received 12 cycles of adjuvant QT with Temozolomide (42 months versus 19 months). Some SG benefits were reported, as well. The median of global life expectancy has not been reached yet in patients with adjuvant QT versus 41 months in those who did not receive it ($p<0,003$)29.

6.2.3.- First line, Grade III Gliomas with IDH 1 and 2 natives, NOS Anaplastic Astrocytoma or NOS Anaplastic Oligoastrocitoma

This subgroup has the worst prognosis, and still there are no data available regarding specific effects in patients with Native IDH (CATNON study). The suggestion is to treat them with RT-QT, according to Stupp´s Protocol, although it could also be treated with sequential RT-QT, with Temozolomide in 12 cycles[29].

Second Line

Management of recurrent anaplastic glioma may consider re-operation, re-irradiation and even the use of alkylant agents (Temozolomide/PC or PCV/Lomustine)[24].

6.3.- Glioblastoma (Grade IV Glioma)

First line

The indication of adjuvant therapy must be made based on the patient´s clinical condition and life expectancy probability. This must be made, considering clinical factors such as age, quality of life measured according to Karnofsky´s Scale (KPI) or ECOG, tumor resection grade and mental condition. The definition of weak patient must be taken into account, as for those patients older than 65 years old, and those whose condition do not allow them to perform their self-care (non self-reliant)[30].

A.- Non self-reliant Patients

The suggestion is to refer them to palliative care, a hypo fractioned radiotherapy scheme

(reduction of dosage and duration of the treatment) or palliative radiotherapy[30] may be considered.

B.- Self-reliant Patients older than 65 years old
For GBM carriers who are elderly people, their life expectancy is lower, as they have more aggressive tumors and further complications with their treatment[31]. For patients older than 65 years old, with a KPI higher or equal to 70%, it is recommended to perform hypo fractioned RT with concomitant and adjuvant Temozolomide, as the study EOTRC 26062-22061 stage III reported higher SG with this scheme, when compared with hypo fractioned RT with no chemotherapy (9.5 versus 7.6 months $p<0.0001$)[32]. In case of patients with significant fragility or comorbilities monotherapy may be considered. In RT there is no difference in SG between a hypo fractioned scheme (5.6 months) and the standard scheme (5.1 months)[33]. In elderly people with methylated MGMT, QT monotherapy with Temozolomide[34,35] may be considered.

C.- Self-reliant Patients younger than 65 years old
This is based on Stupp´s 6 work EORTC-NCIC, reporting that RT-QT scheme, concomitant and adjuvant with Temozolomide (Stupp´s Protocol) increases global life expectancy, from 12.1 to 14.6 months, increasing life expectancy percentage to 5 years, in 8% absolute (10 versus 2%), when compared with RT exclusive[6].

Second Line
Management of recurrent GBM considers re-operation, re-irradiation options and use of alkylant agents. Repeating the previously used Temozolomide scheme may be considered, if the progression occurs 5 months after completion of the treatment[23]. The EORTC 26101 study compared the treatment with Lomustine (Monotherapy) vs Lomustine plus Bevacizumab, and no advantages in SG[24] were reported. The Belob´s study is a Stage II study with three parallel branches. It reported a similar survival rate, before the use of Lomustine and Bevacizumab, as a monotherapy[36].
The summary of the aforementioned medical-surgical management is described in Figure 1.

7- FOLLOW UP
Follow up is for life21. It is recommended to perform control with (BMR) at decreasing intervals. (BMR) must include axial acquisition of the T2, FLAIR sequences, diffusion, T2 GRE or another magnetic susceptibility sequence (SWI), T1 SE with and with no contrast. If it is possible, include volumetric T1 sequences with contrast and DCE, DSC and/or ASL perfusions. Use of perfusion techniques in follow up of treated gliomas allow to have a better differentiation among phenomena attributable to treatment v/s tumor progression[37].
Encephalon disturbances, secondary to therapy, represent a spectrum including early onset (pseudo progression) as well as late installation (radio necrosis). Pseudo progression is defined as the progression of new contrast uptake lesions, usually associated to edema, which are produced within the first 6 months after completing the treatment, and can improve or heal spontaneously[38]. On the other hand, onset of lesions due to radio necrosis usually occurs between 9 to 12 months after completing the treatment. Both processes correspond to the ends of a continuous named as "treatment-related changes". Even though these are different physio pathological mechanisms, maybe their most relevant clinical differentiations are that those patients who evolve with pseudo progression have a more favorable prognosis, while those who develop radio necrosis experience a more stressed neurological impairment; therefore, with a worse functional prognosis.

8.- GENERAL SYMPTOMATIC MANAGEMENT

The main medicament for managing cephalea and deficit symptoms are corticoids. A dosage of 16, 8 and 4 mg of Dexamethasone have been compared with a very similar effect, after a week of treatment. The suggestion is to start a higher dosage, to be reduced later to one dosage, aimed to mitigate symptoms or the recession[39]. Paracetamol or anti-inflammatory drugs may be associated on an hourly basis. Drugs derived from opioids must also be considered for this type of pain[40].

It is very important to state that rehabilitation is aimed to get functional improvement.

Figure 1

Gliomas Grade II	Mutated IDH	Low Risk	Observation
		High Risk	Sequential RDT-QMT with PCV/PC/Temozolomide QMT con PCV/PC /Temozolomide
	Native IDH	RDT-QMT,a ccording to Stupp´S Protocol	
		Sequential RDT-QMT PCV/PC/Temozolomide	
Gliomas Grade III	Mutated IDH and Co-deletion 1p19q or NOS Anaplastic Oligodendroglioma	Sequential RDT-QMT with PCV/PC/Temozolomide	
	Mutated IDH, and with no Co-deletion 1p19q	Sequential RDT-QMT with Temozolomide	
		RDT-QMT, according to Stupp´s Protocol	
	Native IDH or NOS Anaplastic Astrocytoma	RDT-QMT According to Stupp´s Protocol	
		Sequential RDT-QMT with Temozolomide	
Glioblastoma (GBM) or Glioma Grade IV	Weak Patient	RDT Scheme for Fragile Patient	
		Standard Risk Patient <65 years old	
	RDT-QMT, according to Stupp´s Protocol		
	Patient >=65 years old KPI >=70%	RT hypofractioned	
		RDT-QMT, according to Stupp´s Protocol	
		RDT hypofractioned with Temozolomide	

Managing a healthy exercise program is a suggested. This routine could be performed by kinesiologists or physical education teachers with an expertise on oncological patients[39].

On the other hand, regarding infections, pneumonia caused by pneumocistis jirovecii appears between 1.7 and 6.2% of these patients, as a result of a combined treatment of QT and corticoids. Use of prophylaxis with Co-trimoxazole-Sulfamethoxazole is recommended in QT patient, especially if they use corticoids and have lymphopenia[39].

Regarding the possibility of epileptogenic activity, use of antiepileptic drugs during the period perioperative is recommended. In case there is no crisis at the onset, the antiepileptic drug must be removed, seven days after surgery. In case of a crisis, use of anticonvulsants with non enzymatic inducing agents[41] is suggested. Valproic acid increases myelosupression, as it

is used along with Temozolomide and Lomustine[41]. In advances stages patients use to have deglutition disorders. Sublingual Clonazepam or subcutaneous Midazolam or the use of endovenous drugs[41] is recommended (See Table 2).

Fatigue, nauseas and constipation are frequent symptoms. Any action aimed to improve fatigue, such as exercise and use of drugs (Modafinil or Methylphenidate), are partially effective, and have a low level of evidence[42].

Deliriums can be treated with Olanzapine, Risperidone, Aripiprazole and Haloperidol which have proven their effective use. At final stages sedation[43,44] is recommended.

In case of unconsciousness, use of stomach tubes or gastrostomy is not recommended, as they are useless, because quality of life is not improved and it favors bronchial aspiration[44,45].

9.- CONCLUSIONS AND FUTURE PERSPECTIVES

This joint work, made with a team of national experts, and by selecting the best evidence available, we have reviewed the main progress in diagnosis and management of this sanitary issue. Likewise, we could also detect the main constraints in national/international medical/scientific knowledge, as well as to review current local challenges, in order to update our knowledge regarding integral management of these patients.

In that context, it is important to highlight the following facts; (i) there is a high need to implement an updated record of tumors of the central nervous system (ii) imagery diagnostic techniques are complex and require leading edge technology and highly trained professionals, (iii) development and implementation of molecular/accuracy oncology is a must for current clinical practice and control of gliomas in adults, (iv) modern neurosurgery must be supported by interventional imagery and intraoperative clinical neurophysiology, (v) to date there are just a few therapeutical implementations (biological), if compared with other oncological areas. In this sense, more advances are expected in the short term.

Finally, it is necessary to consolidate multidisciplinary oncological teams aimed to develop, at the same time, a systematic welfare labor, as well as a robust research activity, with a clear basic-clinical and/or translational approach.

Table 2. Dosage and Frequency of Antiepileptic drugs used

Conserved Deglutition	Daily Dosage	Frequency
Levetiracetam	1000- 3000mg	every 12 hours
Clobazam	10- 30 mg	every 12 hours
Lacosamida	200- 400mg	every 12 hours
Lamotrigina	100- 300mg	every 24 hours
Valproic Acid	800- 2400mg	every 8 hours
Phenytoin	200- 600mg	every 12 hours
Carbamazepine	400- 1800mg	every 12 hours
Deglutition Disorder		
Sublingual Clonazepam	0,5mg-1mg	every 6 hours
Subcutaneous Midazolam	From 5mg	Variable

mg: milligram

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